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HYPERINSULINEMIA SECONDARY TO AN ADENOMA OF THE PANCREAS

REPORT OF A CASE WITH OPERATIVE CURE

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Since the liberation of insulin, by the monumental work of Banting and Best [1] in 1922, the clinical syndrome of hypoglycemia or insulin shock has become a well recognized medical entity and one with which the average clinician is now fully familiar.

That such a state, so-called hyperinsulinemia, might arise spontaneously within the human body as a result of the overproduction of insulin by the cells of the islands of Langerhans was first suggested by Harris [2] in 1924.

Krause,[3] Marsh,[4] Gammon and Tenery,[5] and Heyn [6] have reported cases presenting the clinical picture of recurrent hypoglycemia in which the blood sugar values during the attacks ranged from 33 to 60 mg. per hundred cubic centimeters.

Since none of the foregoing cases has come to autopsy or been surgically explored, the hypoglycemia cannot be irrefutably ascribed to hyperinsulinemia resulting from hyperplasia or tumorous proliferation of the islet cells.

Finney and Finney, Jr.,[7] and Allan [8] reported two cases in which the symptoms of hyperinsulinemia were present, but at operation no

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2. Harris, S.: Hyperinsulinism and Dysinsulinism, J. A. M. A. **83**:729 (Sept. 6) 1924.

3. Krause, F.: Hyperinsulinism with Hypoglycemic Syndrome, Klin. Wchnschr. **9**:2346, 1930.

4. Marsh, H. E.: Hyperinsulinism with Report of Cases, Wisconsin M. J. **30**:340, 1931.

5. Gammon, G. D., and Tenery, W. C.: Hypoglycemia; Clinical Syndrome, Etiology and Treatment; Report of Case Due to Hyperinsulinism, Arch. Int. Med. **47**:829 (June) 1931.

6. Heyn, Louis G.: Hyperinsulinism, J. A. M. A. **98**:1441 (April 23) 1932.

7. Finney, J. M. T., and Finney, J. M. T., Jr.: Resection of the Pancreas, Ann. Surg. **88**:584, 1928.

8. Allan, F. N.: Hyperinsulinism, Arch. Int. Med. **44**:65 (July) 1929.

gross abnormality of the pancreas was found. In each case a portion of the pancreas was resected. It was believed that there was some amelioration of the patients' symptoms.

The association of hypoglycemic manifestations with marked hypertrophy of the islands of Langerhans has been demonstrated by the cases reported by Phillips [9] and Gray and Feemster.[10]

Warren,[11] in 1926, noted the occurrence of tumorous proliferation of the islet cells during his microscopic studies of pancreatic sections but failed to attach any clinical significance to the presence of these adenomas.

Wilder and his associates [12] at the Mayo Clinic correlated this tumorous proliferation of the islands of Langerhans with the clinical syndrome of hypoglycemia.

Thalhimer and Murphy,[13] McClenahan and Morris,[14] Frank,[15] and Smith and Seibel [16] reported four additional cases which presented the clinical picture of hypoglycemia. In each instance, autopsy revealed a definite adenoma in the pancreas composed of island tissue.

The available literature presents three cases reported by Howland and co-workers,[17] Carr and his collaborators,[18] and Womack and his associates,[19] in which a preoperative diagnosis of hyperinsulinemia, with hypoglycemia, secondary to a tumor involving the islands of Langerhans has been confirmed by the demonstration of the tumor and its enucleation

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9. Phillips, A. W.: Hypoglycemia with Hypertrophy of the Islands of Langerhans, J. A. M. A. **96**:1195 (April 11) 1931.

10. Gray, S. H., and Feemster, L. C.: Compensatory Hypertrophy and Hyperplasia of the Islands of Langerhans in the Pancreas of a Child of a Diabetic, Arch. Path. **1**:348 (March) 1926.

11. Warren, S.: Adenomas of the Islands of Langerhans, Am. J. Path. **2**:335, 1926.

12. Wilder, R. M.; Allan, F. N.; Power, M. H., and Robertson, H. E.: Carcinoma of the Islands of the Pancreas, J. A. M. A. **89**:348 (July 30) 1927.

13. Thalhimer, W., and Murphy, F. D.: Carcinoma of the Islands of the Pancreas, J. A. M. A. **91**:89 (July 14) 1928.

14. McClenahan, W. U., and Norris, G. W.: Adenoma of the Islands of Langerhans with Associated Hypoglycemia, Am. J. M. Sc. **177**:93, 1929.

15. Frank, H.: Fatal Hypoglycemia in Adenoma of the Pancreas, Deutsches Arch. f. klin. Med. **171**:175, 1931.

16. Smith, M. G., and Seibel, M. G.: Tumors of the Islands of Langerhans and Hypoglycemia, Am. J. Path. **7**:723, 1931.

17. Howland, G.; Campbell, W. R.; Maltby, E. J., and Robinson, W. L.: Dysinsulinism, J. A. M. A. **93**:674 (Aug. 31) 1929.

18. Carr, A. D.; Parker, Robert; Graves, E. W.; Fisher, A. O., and Larrimore, J. L.: Hyperinsulinism from B-Cell Adenoma: Operation and Cure, J. A. M. A. **96**:1363 (April 25) 1931.

19. Womack, N. A.; Gnagi, W. B., Jr., and Graham, E. A.: Adenoma of the Islands of Langerhans with Hypoglycemia, J. A. M. A. **97**:831 (Sept. 19) 1931.

at the time of operation with complete restoration of normal carbohydrate metabolism during the postoperative interval.

Cushing,[20] in his Lister Memorial Lecture, referred to a case of hyperinsulinemia secondary to an adenoma of the pancreas that was then under observation at the Peter Bent Brigham Hospital. The details of this case are, we understand,[21] now being prepared for publication.

REPORT OF CASE

The case which we wish to report first came under our observation on Oct. 13, 1931.

History.—A. R., a 33 year old Mexican, was brought into the accident ward of Cleveland City Hospital with the following history: At 7 p. m. the night before he had been picked up from the street by the police as an "alcoholic" and taken to the station house overnight. He had apparently fallen, striking his head on the sidewalk, for he had a contusion over his right eye and was in a semiconscious state when first found. He failed to regain consciousness during the night, however, and was therefore brought to the hospital.

Physical Examination.—The patient was a stuporous, middle-aged Mexican, who responded to questions only by mumbling. There was a contusion over the right eye with a small hematoma, but no laceration of the scalp. There was no evidence of hemorrhage from the cranial orifices. The pupils were moderately dilated and slightly unequal, the right being larger than the left. Reaction to light and accommodation was only slight. The eyegrounds were normal. There was no nuchal rigidity. The heart and lungs were normal. Blood pressure was 112 systolic and 52 diastolic. Examination of the abdomen, genitalia and rectum revealed no abnormalities. The reflexes were physiologic except the Babinski, which showed bilateral dorsiflexion of the great toes without flaring of the other toes.

Laboratory Data.—On admission the urine was normal. The hemoglobin was 100 per cent, and the white blood count 16,000. The temperature was 37.2 C. (98.9 F.), the pulse rate, 80, and the respirations, 20. Spinal puncture yielded a clear fluid, with a pressure of 2 mm. of mercury, which contained 2 cells. The Pandy test was negative.

The patient could not be aroused from his semistupor, and diagnosis of alcoholism with cerebral edema (?) and fracture of the skull was made.

As a means of combating the supposed cerebral edema, hypertonic dextrose was given intravenously. The patient instantaneously aroused from his stupor, sat upright, and appeared to be entirely rational. Questioning failed to elicit any history of previous similar attacks. No history of diabetes or insulin usage could be obtained.

On the morning of the day after admission the patient was again in coma. Chemical examination of the blood at that time showed a blood sugar of 23 mg. per hundred cubic centimeters, urea of 32 mg., creatinine of 1.9 mg. and a carbon dioxide-combining power of 60. Dextrose was given intravenously with the same phenomenal effect. A tentative diagnosis of hyperinsulinemia, with hypoglycemia, secondary to a tumor of the islands of Langerhans was then made.

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20. Cushing, Harvey: Lister Memorial Lecture, Lancet **2**:119, 1930.
21. Cushing, Harvey, and Newton, F. C.: Personal communications.

Blood was withdrawn at three hour intervals during the day; no food was given other than dextrose administered intravenously. The blood sugar levels are recorded in table 1.

The patient was then placed on a measured diet of 1,800 calories, carbohydrate 60 Gm., protein 60 Gm., fat 140 Gm. On this diet he continued to go into hypoglycemic shock at six to eight hour intervals.

During each of these seizures the patient showed the plantar response first called to our attention by Hart and Bond [22] as a diagnostic aid in differentiating between insulin shock and diabetic coma. In their experience this extensor response was not elicited during diabetic coma unless the patient had some associated organic disease involving the pyramidal tract. In insulin shock, on the other hand, the extensor response had been obtained in two instances. They conclude, therefore,

TABLE 1.—*Initial Blood Sugar Values*

Time	Blood Sugar Level, Mg. per 100 Cc.	Intravenous Dextrose, Gm.
8:00 a.m.	23	25
12:00 noon	43	
3:00 p.m.	23	25
6:00 p.m.	88.4	
9:00 p.m.	28.6	25

TABLE 2.—*Initial Dextrose Tolerance Test*

Time	Blood Sugar Level, Mg. per 100 Cc.	Intravenous Dextrose, Gm.
7:15 a.m. (fasting specimen)	25	25
7:45 a.m.	76	
8:15 a.m.	229	
8:45 a.m.	205	
9:15 a.m.	210	
9:45 a.m.	216	
10:15 a.m.	195	
10:45 a.m.	137	

that the presence of the plantar response in a comatose diabetic person on insulin treatment should be accepted as evidence that the coma is due to insulin shock.

A dextrose tolerance test (table 2) was done on October 16. This, as in the recorded cases, showed a diabetic type of curve. Urinalyses, however, failed to reveal any sugar or acetone in the urine.

A study of the gastro-intestinal tract was made in an attempt to visualize a pancreatic tumor. The fluoroscopic examination and films of the stomach and duodenum showed no evidence of an organic lesion within these viscera or of displacement by an extra gastric growth.

Pituitary dysfunction, as a cause of the recurrent hypoglycemia, was eliminated by the roentgenologic demonstration of a normal sella turcica and the absence of any clinical evidence of pituitary dystrophy.

Plates of the skull showed no evidence of fracture.

22. Hart, P. M. D'A., and Bond, H. P.: The Diagnostic Value of the Plantar Response in Insulin Coma, Brit. M. J. **1**:895 (May 18) 1929.

In order to prove that the hypoglycemia was not due to inadequate glycogen in the liver, 1 cc. of epinephrine hydrochloride was given subcutaneously on October 21. The response is recorded in table 3.

It now seemed reasonably well established that this man's symptomatology was due to a persistent hyperinsulinemia. An exploratory laparotomy was, therefore, advised.

In preparation for operation, 1,500 cc. of 5 per cent dextrose was given subcutaneously and 100 cc. of 50 per cent dextrose intravenously.

Operation and Course.—An exploratory laparotomy was done by Dr. S. O. Freedlander on November 2 with the patient under spinal anesthesia. When the pancreas was exposed a small, purplish, cystlike structure, 1.5 to 2 cm. in diameter, was found projecting from its anterior surface about a half inch above the inferior border of that organ near its midportion. The remainder of the pancreas was

TABLE 3.—*Preoperative Response to Epinephrine*

Time	Blood Sugar Level, Mg. per 100 Cc.	Medication
1:45 p.m.	44	1 cc. epinephrine hydrochloride subcutaneously
2:15 p.m.	63	
2:45 p.m.	49	

TABLE 4.—*Daily Postoperative Blood Sugar Levels*

Time	Blood Sugar Level, Mg. per 100 Cc.	Condition
11/2/31	99	Immediately postoperative
11/3/31	151	Fasting
11/4/31	119	Fasting
11/5/31	140	Fasting
11/6/31	129	Fasting
11/7/31	116	Fasting
11/9/31	99	Fasting

entirely normal in gross appearance, and palpation failed to reveal any other similar nodules. Examination of the adjacent viscera disclosed no evidence of metastases. The cystic nodule was then carefully shelled out of the pancreas by blunt dissection. The embedded surface did not appear to be well encapsulated and a small portion of the surrounding pancreatic tissue was removed with the specimen.

The patient remained rational and cooperative during the course of the operation. A specimen of blood withdrawn immediately postoperatively showed a blood sugar of 99 mg. per hundred cubic centimeters. The patient was then given an additional 25 Gm. of dextrose intravenously, the last required during the forty days that he remained in the hospital.

Postoperatively, he was placed on the usual liquid diet, without any additional carbohydrates. Blood sugar estimations during fasting were made daily for the first week. These showed values ranging from a high of 151 on the first postoperative day to a low of 99 a week later (table 4). Thereafter blood sugar determinations were made three times a week. All of the values were found to be within normal limits. The lowest was 76 and the highest 144 mg. per hundred cubic centimeters.

Fifteen days after operation a dextrose tolerance test was done. This still showed a higher than normal rise, but a normal level was reached at the end of the second hour (table 5).

The response to 1 cc. of epinephrine hydrochloride injected subcutaneously, one month after operation, is depicted in table 6.

On the morning of December 6, the patient was placed on the measured 1,800 calorie diet on which he had gone into hypoglycemic coma at six to eight hour intervals prior to the removal of the adenoma. During the ensuing week no signs or symptoms of hypoglycemia became manifest. The daily blood sugar values

TABLE 5.—*First Postoperative Dextrose Tolerance Test*

Time	Blood Sugar Level, Mg. per 100 Cc.	Condition
7:15 a.m.	91.0	Fasting
25 Gm. dextrose intravenously		
7:45 a.m.	251.0	
8:15 a.m.	179.0	
9:15 a.m.	49.3	
10:15 a.m.	44.1	
11:15 a.m.	65.5	

TABLE 6.—*Postoperative Epinephrine Response*

Time	Blood Sugar Level, Mg. per 100 Cc.	Condition
8:30 a.m.	102	Fasting
1 cc. epinephrine hydrochloride subcutaneously		
9:00 a.m.	135	
10:00 a.m.	95	
11:00 a.m.	90	

TABLE 7.—*Final Dextrose Tolerance Test*

Time	Blood Sugar Level, Mg. per 100 Cc.	Condition
8:30 a.m.	96	Fasting
25 Gm. dextrose intravenously		
9:30 a.m.	195	
10:30 a.m.	119	
11:40 a.m.	102	

made during fasting for this week ranged from 76 to 144. At the end of the week of restricted diet the final dextrose tolerance test was made (table 7). This represents an essentially normal response and would seem to indicate that a normal carbohydrate metabolism had finally been established.

The patient's convalescence was uneventful save for the development of a small pancreatic fistula which healed completely prior to his discharge from the hospital on December 12, forty days after excision of the pancreatic tumor. He has remained well and symptom-free during the ten months that have elapsed since his release. There is no external evidence of recurrence and he has been free from seizures.

Pathologic Report.—The specimen consisted of a globular mass of tissue 2 cc. in diameter which weighed about 4 Gm. The surface was irregular and presented

as a slightly lobulated, yellowish-gray, soft tissue resembling the acinous tissue of the pancreas. At one place, over an area about 5 mm. in diameter, this yellowish tissue was absent, and through this capsule there was seen a grayish-white tissue. On section, contained within the pancreatic tissue was a fairly circumscribed nodule about 1.5 cm. in diameter which was made up of a uniform grayish pink, smooth, moist, somewhat translucent tissue. The stroma appeared to be scant. There was no well defined capsule. In places the tumor tissue blended with the pancreatic tissue.

Microscopically, the tumor was made up of round and polygonal cells with eosinophilic, faintly granular-staining cytoplasm and round vesicular nuclei with

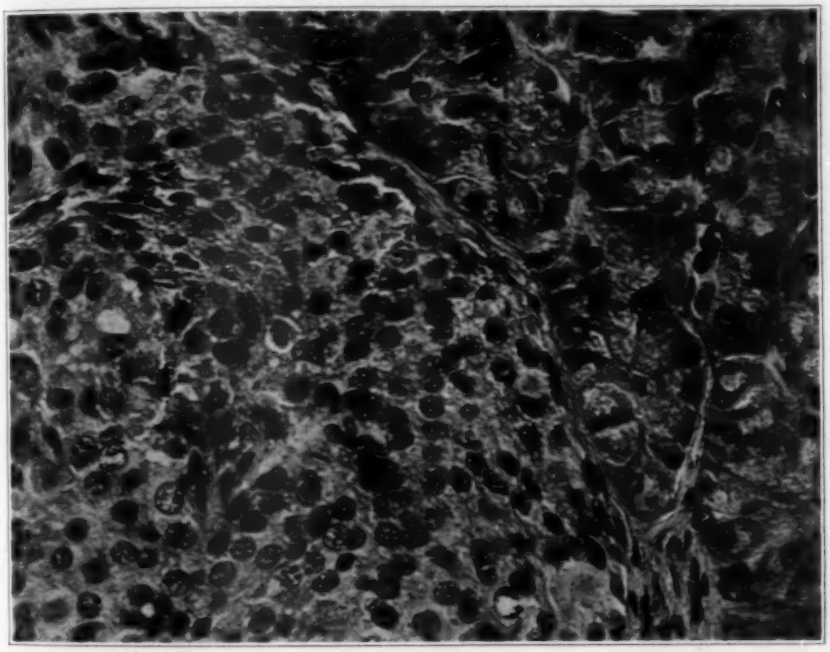

Fig. 1.—The round and polygonal cells of the tumor, separated by thin connective tissue septums, are shown.

prominent nucleoli (fig. 1). The cells grew in compact masses broken up into small alveolar formations by thin vascular connective tissue septums. In places there were wide bands of fibrous tissue interspersed between these alveolar formations, suggesting fibrous replacement of the tumor. In several sections the tumor tissue reached to the free surface where it was seen infiltrating the adjacent fatty tissue. In some areas the tumor cells surrounded small bits of the normal acinous tissue of the pancreas. In other areas there was a suggestion of invasion of the normal pancreatic tissue (fig. 2). The acinous tissue and islands of the pancreatic tissue appeared normal (fig. 3).

The special stains showed the tumor to be made up of uniformly staining cells, chiefly chromophobe, suggesting the alpha type of cell according to the Bensley terminology.

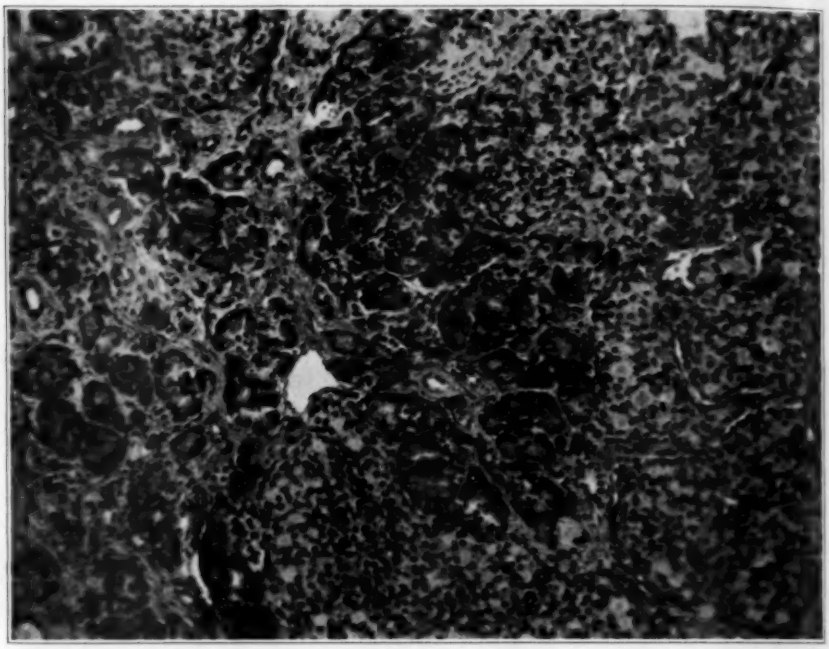

Fig. 2.—Area suggesting invasion of the normal acinous tissue by the tumor.

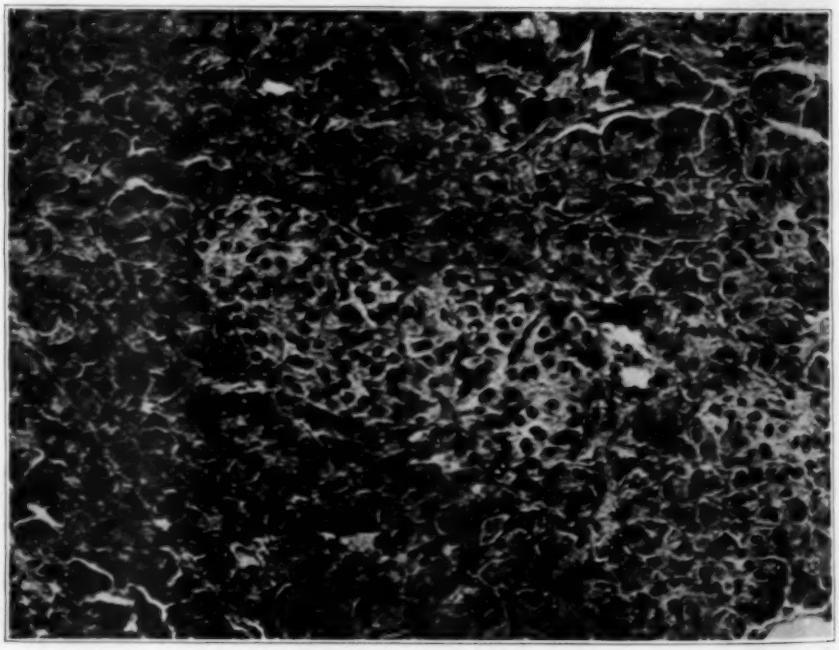

Fig. 3.—Normal acinous tissue and island.

SUMMARY

1. The history and course of a case of hyperinsulinemia with hypoglycemia secondary to a tumor involving the islands of Langerhans has been presented.

2. This case differs from the recorded cases in that the onset was apparently abrupt with complete loss of consciousness and evidence of external injury that caused his symptoms to be attributed to cerebral edema or concussion.

3. During each of his seizures of hypoglycemia, the patient presented the semi-Babinski or extensor response called to our attention by Hart and Bond as a diagnostic aid in differentiating between insulin shock and diabetic coma.

4. The complete absence of hypoglycemic seizures together with the clinical and laboratory evidence of the establishment of a normal carbohydrate metabolism immediately after the excision of the small pancreatic nodule, is, we believe, adequate proof that this man's symptoms were due to the excessive production of insulin by the tumor tissue.

5. The data here presented, together with the clinical and experimental evidence cited in the previously reported cases, suggest again that tumors arising from glandular tissue may in some instances retain the function of the organ or tissue from which they arose.

6. At the present time, exploration with removal of the adenoma, if demonstrable, offers the best chance of clinical cure.

PATHOGENESIS OF ACUTE PANCREATITIS (ACUTE PANCREATIC NECROSIS)

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Introduction
Etiology of Acute Pancreatic Necrosis
Common Channel Theory and Objections to It
Relation of Bile to Acute Pancreatic Necrosis
Nonbiliary Causes of Acute Pancreatic Necrosis
Mechanism of Production of Acute Pancreatic Necrosis
Does Intraglandular Activation of Trypsin Cause Acute Pancreatic Necrosis?
Mechanism of Production of Acute Pancreatic Necrosis by Bile
Summary
Cause of Death in Acute Pancreatic Necrosis
Observations on the Toxicity of Pancreatic Juice
Intraperitoneal Injection of Fresh, Actively Proteolytic Pancreatic Juice
Intravenous Injection of Fresh, Actively Proteolytic Pancreatic Juice
Intraperitoneal Injection of Fresh, Actively Proteolytic Pancreatic Juice, Sterilized by Berkefeld Filtration
Intraperitoneal Injection of Fresh, Actively Proteolytic Pancreatic Juice from the Dog into Mice
Comment
Observations on the Toxicity of the End-Products of Pancreatic Digestion and Autolysis and the Rôle of Bacteria in the Toxemia of Acute Pancreatic Necrosis
In Vivo Autolysis of Dog Pancreas Complicated by the Presence of Bacteria Commonly Found in the Uncontaminated Gland
In Vivo Autolysis of Sterile Fetal Pancreas
Intraperitoneal Digestion of Sterile Autoclaved Pancreas
Toxicity of the End-Products of the Aseptic Digestion of Pancreas in Vitro
Intraperitoneal Digestion of Autoclaved Pancreas by Sterile Pancreatic Juice
Comment
Observations on the Effect of Acute Pancreatic Necrosis on Certain Constituents of the Blood
Treatment
Conclusions

From the Department of Surgery of the University of Chicago.

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INTRODUCTION

It is our purpose in the present paper to present data derived from both the experimental laboratory and the clinic, together with an analysis of a part of the accumulated literature, in an attempt to clarify further the problem of the pathogenesis of acute pancreatitis. At first glance, it might appear that some of the questions raised are of purely academic interest, but it is our hope that a careful examination of them may afford new avenues of approach to a better understanding of this difficult and highly important problem. All recent writers on the subject are agreed in deploring the present appalling mortality associated with the disease, and this fact alone should stimulate interest in all the various factors which may operate to produce it. In a recent paper, von Schmieden and Sebening (1927) quoted this pertinent question, "Warum sterben immer noch so viele Menschen an dieser plötzlichen und furchtbaren Krankheit"? (Why do so many people still die of this sudden and fearful disease?) An extensive experimental investigation has been conducted, and a great many significant clinical observations have been made. Much has been accomplished, and a fairly adequate surgical treatment has been developed. Indeed, it is possible that the limit has been reached in the way of operative procedure, and that a further lowering of the excessive mortality must come from another direction. The fact that the pancreas is an organ indispensable to life, the fact that it is situated in the upper part of the abdomen in close proximity to the extensive celiac nerve plexus, and the fact that it is in a region where the absorption of toxic chemical products occurs with unusual facility operate to limit the scope of surgical treatment.

While it is probable that edema and hemorrhage of the pancreatic parenchyma are frequent findings and may indeed represent early stages in the disease, it is the necrosis, sometimes limited but often extensive, that is the significant change. It has been clearly demonstrated by Archibald (1929) and confirmed by ourselves that the entrance of bile into the pancreatic duct may produce an immediate and intense edema, which later entirely subsides or in more severe cases is followed by cellular necrosis. This edema probably produces pain either through tension on the delicate pancreatic capsule or through mechanical injury to the nerves of the neighboring sympathetic visceral plexus. The symptoms have been fairly clearly defined by Zoepffel (1922), Archibald (1929), Stetten (1930) and others. Collapse and death do not occur unless necrosis succeeds the edema. It is likely that the hematogenous infection of the pancreas seen occasionally in acute epidemic parotitis is an acute pancreatitis with edema, but it is only rarely followed by necrosis.

It is thus probable that while edema and hyperemia may precede the necrosis in most cases, they are not necessarily followed by necrosis.

and they produce effects by a mechanism different from that by which necrosis is produced. There is no question that the vascular collapse, signs of toxemia and later death are the direct result of the necrosis of the pancreatic parenchyma. The term acute pancreatic necrosis is perhaps preferable to acute pancreatitis or acute hemorrhagic pancreatitis.

The fundamental questions we may ask ourselves are these: What causes the sudden extensive necrosis of the pancreas? How does a sudden extensive necrosis of the pancreas cause death? These questions are partly answered in the accumulated clinical literature if the data can be properly evaluated and in a somewhat more precise way by the direct controlled experiment.

ETIOLOGY OF ACUTE PANCREATIC NECROSIS

Agents which naturally come to mind, such as direct injury from trauma, interference with the blood supply to the pancreas through injury, thrombosis or embolism, and infection at least by way of the blood stream as in septicemia, pyemia or lodgment of infected emboli, can apparently account for a small minority of the total cases in which careful study has been made. It is significant, however, that undoubted cases have been reported in which each one of these factors has operated to produce an entirely characteristic picture of the disease. Likewise, it has been possible to reproduce the disease in the experimental animal by practically any method that insures a sudden and fairly extensive necrosis of the pancreatic parenchyma. These facts are of great importance when we come to consider the second question, namely, the cause of death resulting from pancreatic necrosis, but are of less significance in the present problem.

COMMON CHANNEL THEORY AND OBJECTIONS TO IT

The frequent association of acute pancreatic necrosis and biliary tract disease has been uniformly commented on. This prevailing opinion is amply supported by statistical evidence. Thus, Egdahl (1907) reported gallstones in 42 per cent of a series of cases of acute pancreatitis; von Schmieden and Sebening (1927), in 69.8 per cent, and Eliason and North (1930), in 71 per cent. One can hardly doubt that a patient with antecedent cholelithiasis and chronic cholecystitis is more liable to develop the disease than a normal person. It is of interest, therefore, to scrutinize carefully the evidence that has accumulated which may offer an explanation for this widely accepted and probably correct clinical observation. The theory most commonly advanced to account for this frequently noted association of acute pancreatic necrosis and biliary tract disease, the so-called common channel theory of Opie, asserts that the necrosis is due to the passage of bile over into the pancreatic duct.

Its possibility is absolutely dependent on an anatomic arrangement of the opening of the ducts into the diverticulum of Vater so that the lodgment of a small gallstone (Opie 1901, 1904, 1910) in the ampulla, a spasm of the sphincter of Oddi (Archibald 1918, 1919) or an acute edema of the duodenal mucosa in the region of the ampulla (Baló and Ballon, 1929) can close the natural opening of both ducts in the duodenum and convert them into a common continuous channel. The evidence on this point is somewhat conflicting. Opie (1904) reported that in 89 of 100 bodies examined, or 89 per cent, the common bile duct and the duct of Wirsung joined before they entered the duodenum at the papilla of Vater. Baldwin (1911) found that in 70 of a series of 90 cases, or 77 per cent, the ducts anastomosed before emptying into the duodenum. Mann and Giordano (1923), on the other hand, concluded that in only 3.5 per cent of cases was the anatomic arrangement of the ducts such as to permit the development of a common channel by obstruction at the papilla. Cameron and Noble (1924) reported that in 75 per cent of people a calculus lodged in the ampulla could convert both ducts into a common channel and permit a reflux of bile into the pancreas. Hozapfel (1930) reported that in 20 per cent of 50 bodies studied the ducts united and presented a common opening in the same papilla, whereas in 60 per cent they opened separately into the same papilla.

These statistical studies were all made on normal persons. It is unfortunate that we have no satisfactory data with regard to the arrangement of the ducts in patients with acute pancreatitis. It is possible or probable, according to Moynihan (1925), that a higher percentage of these would display a common channel. The meager published data seem to indicate the reverse. However, it is apparent that many cases of acute pancreatitis in which the bile and pancreatic ducts empty separately and at some distance apart in the duodenum have been described in the literature chiefly because in the experience of the author they represented exceptional instances.

The studies of Cameron and Noble (1924) were made on fresh cadavers, and the direct experiment of causing a small biliary calculus to lodge in the ampulla and then determining the patency or continuity of the bile and pancreatic ducts by making a cast of Wood's metal is convincing and should be less subject to error in interpretation than dissection observations on fixed tissues. However, even if we agree with these authors that in a majority of patients it is anatomically possible for the lodgment of a small stone to convert the common bile duct and duct of Wirsung into a common channel, it is not yet clear that bile will necessarily pass into the pancreas.

Theoretically, at least, it might seem that the direction of flow should depend on the relative pressures developed in the duct system of

each gland. Considerable effort has been expended to determine these pressures in the experimental animal. Mann and Giordano (1923) concluded that the secretory pressure of bile might reach from 350 to 375 mm. of bile, whereas the secretory pressure of the pancreatic juice did not exceed from 260 to 300 mm. of water, a finding in harmony with the observations of Herring and Simpson (1909) on the anesthetized dog. Granted that obstruction at the ampulla would not stop the secretion of either bile or pancreatic juice, and that the duct system was uniformly distensible throughout, this difference in pressure should make possible the passage of bile over into the pancreas. Considerable importance (Judd, 1921; Moynihan, 1925) has been attached to the observation of Mann and Giordano (1923) that during vomiting the pressure in the biliary tract rose to 1,000 mm. of bile, and the suggestion has been made that through such a mechanism vomiting might be thought to cause pancreatic necrosis. It is, however, altogether probable that the general increase in intra-abdominal pressure due to the vomiting would be equally transmitted to the pancreatic ducts and to the biliary channels and no transfer of fluid would occur. Harms (1927) reported that during the height of digestion in unanesthetized dogs the secretory pressure of the pancreas is higher than that of the liver, a finding which would suggest the passage of pancreatic juice over into the biliary channels rather than the reverse.

In view of these conflicting observations, we decided to make measurements of the secretory pressure of the pancreas in unanesthetized dogs provided with a special pancreatic fistula as illustrated in figure 1. Most of the previous determinations have been made on animals under general anesthesia, with a cannula tied in one of the pancreatic ducts and with the remaining ducts either patent or ligated. Both of these procedures, i. e., general anesthesia and cannulation of the ducts, have been found by Babkin greatly to decrease pancreatic secretion. In our preparation the ducts empty normally into a closed pouch of the duodenum, and the experiment may be made during and following the normal ingestion of food and accordingly under optimum physiologic conditions. The following protocol represents a typical experiment of this type.

Dog 732.—Feb. 15, 1931: A special pancreatic fistula, as illustrated in figure 1, was made in December, 1930. The condition of the animal was excellent; the fistula was water tight, and from 600 to 900 cc. of pancreatic juice was secreted in twenty-four hours. At 1 p. m., a meal of cooked meat was given. At 3 p. m., pancreatic juice flowed freely. The cannula was then connected by means of a rubber tube to a tall water manometer with an inside diameter of about 5 mm. The pressure gradually rose with the secretion of pancreatic juice until a maximum was reached. At this time the water in the manometer was raised 81 cm. at the height of inspiration and descended to 57 cm. during expiration.

These figures represent an average of the highest secretory pressures developed by this dog and are a measure of the column of water supported by the pressure in the pancreatic-duodenal sac measured from the level of the sac itself. The great variations in pressure caused by respiration should be noted. It is likely that vomiting would have produced as great a rise in pressure as was observed by Mann and Giordino in the biliary tract. It cannot be denied that a part of the pressure may be due to the secretion of succus entericus in the duodenal sac, but this occurs so slowly as compared with secretion of the pancreatic juice that we estimate it to be a minor factor. More important factors are the general intra-abdominal pressure and that due to the motility of the sac

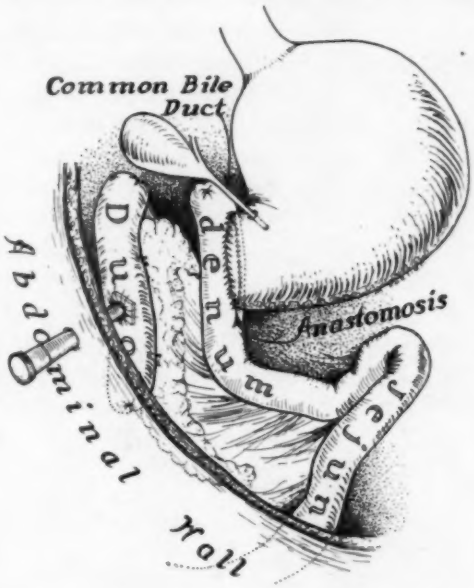

Fig. 1.—Diagrammatic illustration of the type of pancreatic fistula used. The pancreatic ducts empty into the isolated closed segment of the upper duodenum, and an external fistula has been made of this pancreatic duodenal pouch with a special gold plated cannula.

itself. For these reasons, it seems likely that the lower figure (57 cm. of water) obtained after an hour of secretion represents the secretory pressure of the gland, while the higher figures are due to extraneous factors.

It will be noted that this pressure is higher than that obtained by Mann and Giordano (1923) for the secretory pressure of bile, and supports the observation of Harms (1927). It seems to us, however, that these pressures are not the factors which alone determine the direction of flow when the duct systems of the liver and pancreas are converted

into a common channel. Of greater importance is probably the patency of the accessory pancreatic duct of Santorini, and the freedom of anastomoses between it and the branches of the duct of Wirsung within the gland. Granted a free anastomosis between the ducts and a patent duct of Santorini, obstruction at the ampulla might readily reverse the flow in the duct of Wirsung. The secretory pressure of the pancreas would, under these conditions, be ineffectual, and bile might readily pass over into the duct of Wirsung, through the anastomosing channels, and eventually reach the duodenum by way of the duct of Santorini. In cases in which the duct of Santorini is not open or in which there are insufficient anastomoses between the branches of the pancreatic ducts, we should expect from our measurements and those of Harms (1927) to find pancreatic juice passing over into the biliary channels in the event of the production of a common channel at the ampulla. In an examination of 76 specimens of adult human pancreases, Baldwin (1911) found a demonstrable anastomosis between the main and accessory pancreatic ducts within the gland in 66 cases, or 87 per cent. Opie (1904) concluded that such an anastomosis was present in nine tenths of all cases, although in many of these the union was effected by such a minute branch that one duct could not act as an outlet for the secretion of the other. If these conclusions are valid, one can readily understand the passage of bile over into the pancreatic ducts in the majority of patients in whom a common channel is established, whereas in the minority pancreatic juice may pass over into the biliary channels and possibly excite the series of pathologic changes obtained by Wolfer (1931) in the experimental animal. The cases in which pancreatic juice has been found to pass over into the common bile duct or gallbladder and escape in large quantities from a drainage tube placed in the gallbladder or common bile duct after choledochostomy for stone are instructive in this connection. Walters and Marshall (1930) cited a number of such cases and reviewed the literature. It is possible that these instances represent cases in which a common channel has been established and the direction of flow of the secretion determined by the reduction of pressure in the biliary channels artificially produced by the drainage tube. Conversely, it may be argued that a reduction of pressure in the pancreatic ducts occasioned by the anastomoses between the ducts of Wirsung and Santorini might be expected to facilitate the flow of bile over into the pancreas.

Several attempts have been made in the experimental animal to determine the direction of flow of bile when a common channel has been purposely produced. Mann and Giordano (1923) found that in the goat under these conditions bile passed readily over into the pancreas, an observation that we have recently confirmed. Wangensteen, Leven and Manson (1931) produced a common channel in cats and secured the

passage of bile over into the pancreas, particularly after the animals had been given a meal of fat, an observation which suggests that in this animal at least contraction of the gallbladder may be a real factor in determining the biliary pressure. In the dog, the major pancreatic duct empties into the duodenum at a considerable distance from the orifice of the common bile duct, and probably for this reason few attempts have been made to determine the effect of producing a common channel in this animal. We tried to produce such a condition in two dogs by making an anastomosis between the distal ends of the two ducts by means of sutures but failed to secure a patent channel. In 8 dogs a common channel was effected by means of a catheter tied securely into the ends of the common bile duct and major pancreatic duct, respectively. Five of these dogs died in from twenty-two to one hundred and thirty-two hours. Autopsy revealed a generalized peritonitis due to the escape of bile from loosening of the ligature about the bile duct (Andrews, Rewbridge and Hrdina, 1931). In no case was there evidence of bile within the pancreatic ducts. The remaining 3 dogs were killed after thirty-six, fifty-one and fifty-three days, respectively. In 2 of these the bile duct had become reestablished, while in the third it was completely obstructed. The pancreas was normal and entirely free from bile. Wolfer (1931), however, was more successful in experiments of a similar nature performed before those previously detailed were undertaken, and his results seem to indicate that when a common channel is experimentally produced in the dog by intubation of the respective ducts, pancreatic juice usually passes over into the biliary ducts rather than the reverse. The frequency of intraglandular anastomoses between the major and minor pancreatic ducts in the dog is not definitely established. In a few observations we were unable to demonstrate such anastomoses by injecting india ink into the major duct under considerable pressure. The region supplied by the minor duct did not become discolored. As previously noted, it is probable that this absence of anastomoses is significant in determining the direction of bile flow.

Direct evidence with respect to the direction of flow of the secretions in man is practically limited to autopsy observations in cases in which a gallstone has become impacted in the ampulla and a common channel established. To date, the published data indicate that under these conditions bile passes into the pancreatic ducts (Thayer, 1889; Opie, 1901; Fuchs, 1902; Bunting, 1906; Deaver, 1915; Rosenbach, 1918; Guleke, 1924; Grant, 1928). In these cases the staining of the pancreatic ducts by the bile pigment was responsible for the observation. Unfortunately, it is more or less difficult to test for the presence of pancreatic juice in the content of the biliary tract, and doubtless for this reason there is little or no evidence of its occurrence. The impaction of a

gallstone in the ampulla without evidence of pancreatitis has been repeatedly observed at operation. In cases in which recovery has followed removal of the stone, it is not possible to say whether or not a common channel existed.

The conversion of the bile and pancreatic ducts into a common channel in the cases in which it is anatomically possible (in 75 per cent of cases in man according to Cameron and Noble, 1924) is most readily understood when a small gallstone has become impacted in the orifice of the ampulla. A difficulty arises, however, when we come to survey the literature dealing with the occurrence of such impacted calculi in cases of acute pancreatic necrosis. In a series of 437 cases collected by Guleke (1924), a calculus obstructing the ampulla was found in only 1.4 per cent, and in the larger series of 1,278 cases surveyed by von Schmieden and Sebening (1927) a gallstone at the ampulla was recorded in only 4.4 per cent. It is accordingly evident that the production of a common channel in the manner postulated by Opie's theory has occurred in only a small number of instances in which acute pancreatitis has developed, even if we make a reasonable allowance for errors at autopsy or for passage of the stone into the duodenum or backward into the common duct, possibilities recognized by Thayer (1889) many years ago.

A possible solution for this difficulty may be found in the work of Archibald and Brow (1918) and Grant (1928), and in the observations of Baló and Ballon (1929). The former investigators raised the question as to the possibility of a spasm of the sphincter of Oddi converting the ducts in question into a common channel, and submitted evidence obtained for the most part from experiments on lower animals under anesthesia which they interpreted as supporting this view. In somewhat similar experiments, Wangensteen and his associates (1931) were unable to confirm these findings and stated that they were entirely unable to get regurgitation of bile into the pancreatic ducts of cats without organic obstruction at the ampulla. Mann and Giordano (1923) were likewise reluctant to admit the major postulates of Archibald's theory on the basis of insufficient direct evidence and their experience with the lower animals. These criticisms are to the point, but they do not, in our opinion, necessitate abandoning the view altogether, particularly since it is possible that the human biliary tract in the presence of a chronic infection may display disturbances in motility not readily reproduced in the lower animal. There is considerable clinical evidence that cardiospasm and pylorospasm (of a degree not reproducible in animals under general anesthesia) are not infrequently seen in patients with chronic gallbladder disease, and it seems consequently reasonable that hypermotility or spasm might likewise exist in the biliary tract itself, at least so far as its musculature is not destroyed.

Baló and Ballon (1929) submitted evidence indicating that swelling of the papilla duodenalis major in simple catarrhal jaundice may obstruct the pancreatic duct and lead to the retention of pancreatic juice. The possibility that a similar swelling may exist in some cases of chronic biliary tract disease and if sufficiently peripheral may produce a common channel might well be considered by those engaged in postmortem examinations and effort bent to obtain autopsies immediately after death in cases of acute pancreatic necrosis for definite evidence. The importance of the common channel and of the bile factor in acute pancreatitis in man can be determined only by such careful postmortem examination and by chemical tests with respect to the presence of biliary constituents in the ducts or substance of the necrotic pancreas.

RELATION OF BILE TO ACUTE PANCREATIC NECROSIS

The common channel theory as an explanation for the frequent association of chronic gallbladder disease and acute pancreatic necrosis has been brought into question by the discovery of cases in which both diseases have been present and in which the orifices of the common bile duct and the pancreatic duct have been found so far apart in the duodenum that a common channel could not have been formed. Such instances have been reported by Johnstone (1907, 4 cases) and Dardinski (1931, 2 cases) and doubtless many others. These findings, we believe should not be interpreted as disproving the truth of Opie's theory, since they prove only that it is insufficient to explain these particular cases. It becomes, however, necessary to search for other possibilities of extension to the pancreas from a diseased gallbladder. In this connection it should be recalled that acute pancreatic necrosis has occurred in persons with no disease of the biliary tract, the exciting agents having been hematogenous infection, thrombosis or embolism, trauma or other factors. It is not improbable that these factors have occasionally produced acute pancreatic necrosis in patients with gallstones without there being any relation between the two diseases. Such cases would obviously be confusing.

An alternative to the common channel theory, which conforms with the observed increased incidence of acute pancreatitis in patients with gallbladder disease, asserts that the former disturbance has its origin through the extension of infection from the wall of the gallbladder to the pancreas by way of the lymphatics. It has been supported by the work of Maugeret (1908), Deaver and Sweet (1921), Deaver and Pfeiffer (1921), Graham (1922) and Judd (1921). The beneficial results obtained in many cases of acute pancreatitis by cholecystectomy and common duct drainage without direct attack on the pancreas have been thought to support this view. This hardly follows, since drainage

of the common duct would reduce the biliary pressure and, in the event of a common channel, stop the further passage of bile into the pancreas or even make possible a drainage of the pancreatic ducts. A serious objection to the lymphatic extension theory is found in the complete failure to secure pancreatic necrosis in experimentally produced acute bacterial cholecystitis in animals (Kaufmann, 1927) and its rare occurrence in acute infections of the gallbladder in man. Both Grant (1928) and Wangensteen (1931) called attention to the relative safety of the nonoperative treatment of acute cholecystitis, and remarked that if lymphatic extension were a prominent factor it should occur in these acute cases more commonly than in the chronic infections. The validity of the theory and the proportion of cases of acute pancreatitis in which it accounts for the pathogenesis can be determined only by adequate bacteriologic examination at the operating table or in the postmortem room. Cultures of the bile, of the wall of the gallbladder, of the pancreas, and of the intervening tissues and lymph glands should be instructive. To our knowledge such studies have not been made.

The problem seems to resolve itself somewhat as follows: It is probable that approximately 60 per cent of the cases of acute pancreatic necrosis in man arise in patients with antecedent chronic disease of the bile tract. On the basis of the statistical information available, it is likely that in 10 per cent of these a common channel developed as the result of the impaction of a gallstone in the ampulla, and bile passed over into the pancreas. For the remaining 50 per cent comprised in this group, we must assume that a common channel developed as a result of spasm or swelling of the sphincter of Oddi, or else that bile played no direct rôle in the cause of the necrosis. If we assume that a common channel developed in the large majority of these as a result of abnormal motility of the sphincter, then the bile factor becomes of great importance in the pathogenesis of acute pancreatitis. If we adopt the reverse view, then we must account for the high incidence of pancreatitis in patients with gallstones on some other basis, presumably the extension of infection. As will be seen later, it has been amply demonstrated that the passage of bile over into the pancreatic ducts can produce acute pancreatic necrosis in animals, whereas it has been difficult or impossible to produce it by any type of experimental infection.

NONBILIARY CAUSES OF ACUTE PANCREATIC NECROSIS

There remains, however, a group of cases, approximately one third of the total, in which no evidence of gallbladder disease has been found. This group, together with the few cases discussed before in which the bile and pancreatic ducts were found to empty separately into the duodenum, proves that a fatal pancreatic necrosis can arise entirely independent of bile. The occurrence of typical cases of acute pancreatic

necrosis as a result of hematogenous infection of the pancreas is clearly indicated in the literature. Egdahl (1907), in a review of 105 cases of acute pancreatitis, cited 11 as a complication of mumps, 2 as occurring with typhoid fever, 2 with appendicitis, 1 with boils, 1 with malaria, 1 with syphilis, and 1 with pulmonary tuberculosis. McCrae (1925) reported acute pancreatitis as a complication of typhoid fever, scarlet fever, diphtheria and smallpox. The literature, mostly French, dealing with the incidence of acute pancreatitis as a complication of mumps, has been reviewed by Brahdy and Scheffer (1931). In 171 of 7,054 cases of mumps, the diagnosis of acute pancreatitis was made. In many of these cases the pancreatitis was mild, and it is likely that a considerable error in diagnosis must be allowed. Nevertheless, the statistics establish the fact that acute pancreatic necrosis may, under appropriate conditions, arise as a result of hematogenous infection. It is equally well established that trauma alone may cause typical pancreatic necrosis. Such cases have been reported by Lattes (1913) and by Holmes (1922). Katz and Winkler (1898) produced the disease in dogs by means of mass ligature of the blood supply and ducts and gross injury to the parenchyma, a result repeatedly confirmed by later workers. The theory that acute pancreatic necrosis may be produced by vascular injury, notably embolism or thrombosis, as advanced by Gilbert, Lepine and others is supported by the occasional occurrence of such cases in the clinic (Egdahl, 1907, 2 cases). The disease is, however, not readily produced in the lower animal by the ligation of the blood supply to the pancreas (Guleke, 1904, and our own experiments).

MECHANISM OF PRODUCTION OF ACUTE PANCREATIC NECROSIS

We have considered thus far the possible production of acute pancreatic necrosis in man by the introduction of bile into the pancreatic ducts, the extension of infection to the pancreas by way of the lymphatics, ducts or blood stream, direct trauma and vascular injury. According to the view of many students of this problem, all of these factors bring about the ultimate necrosis of the pancreas in the same manner. It is assumed that they cause the activation of the powerful proteolytic enzyme trypsin while it is still within the pancreatic substance or its ducts, and that the active trypsin then digests away the living pancreas. Sweet (1915) stated this view in dramatic fashion as follows: "There is, however, abundant evidence that this activation of pancreatic juice is not only what 'leads to autolysis of the cells,' but it is just this activated pancreatic juice which is responsible for the entire picture, canvas and frame, glass and signature, of this most acute and terrible intoxication, the whole secret of acute pancreatitis."

According to Moynihan (1925): "In acute pancreatitis, the immediate cause of the gland necrosis is the activation of the pancreatic juice by some agent or other, within the substance of the gland."

DOES INTRAGLANDULAR ACTIVATION OF TRYPSIN CAUSE ACUTE PANCREATIC NECROSIS?

It was demonstrated many years ago by Pavlov, Bayliss and Starling (1904) and others that the proteolytic enzyme of the pancreatic juice is secreted in an inactive form called trypsinogen, and that the pure juice in the duct system of the pancreas has no digestant effect on protein. Chepovalnikov (1899) showed that when this juice comes into contact with a substance, enterokinase, present in the secretion of the duodenal or jejunal mucosa, the trypsinogen becomes converted into the exceedingly active proteolytic ferment trypsin. Subsequent work by many investigators has demonstrated that a wide variety of substances in addition to enterokinase may activate trypsinogen, and indeed that it becomes active on long standing without the addition of extraneous material. The suggestion that this powerful proteolytic ferment is manufactured in an inactive form because otherwise it would cause the immediate digestion of the cell that made it is quite attractive, and it follows that its activation after the pancreatic secretion reaches the lumen of the intestine is innocuous because of a special property of the intestinal mucosa to resist digestion. A somewhat similar argument has been advanced to account for the normal failure of the stomach to digest itself. One may assume then, and this assumption has been generally made, that an activation of the trypsinogen in the pancreatic juice while it is still present in the duct system of the pancreas or in the secreting cells would result in the widespread self-digestion of the gland. Such a mechanism has appeared necessary to account for the great predominance of acute necrosis of the pancreas in comparison with other organs.

In this connection, it should be recalled that the cell membranes appear to be largely composed of lipoids rather than proteins, and it would appear more reasonable to expect destructive effects from fat-splitting enzymes than from those that digest proteins.

In such theories, moreover, there appears to be a misconception of the properties of enzymes. Apparently many writers regard the proteolytic enzymes, pepsin and trypsin, as corrosive chemical substances capable not only of producing a more or less complete disintegration of the protein molecule but of attacking living cells themselves. There is no evidence for such a view. Our knowledge in the highly complex field of enzyme chemistry is still very limited, but at the present time most investigators seem to be agreed that the enzymes are organic compounds, probably protein in nature, manufactured by living cells.

They are true catalysts in that they can only accelerate a reaction which otherwise would take place slowly, while they cannot start a reaction which otherwise would not occur. They may be compared with such an inorganic catalyst as spongy platinum which, when introduced into a mixture of oxygen and hydrogen, greatly increases the speed of combination of these elements, a reaction, however, already going on in the absence of the platinum. The proteolytic ferments merely increase the rate of hydrolysis of proteins produced either by a dilute acid of gastric juice or by the dilute alkali of the pancreatic secretion. The problem of the resistance of living tissues to either gastric or pancreatic digestion is primarily one of resistance to the toxic effect of dilute acid or alkali on protoplasm.

We have fairly direct evidence that this is the case with gastric juice. Claude Bernard (1859) reported that the leg of a living frog would be digested away if introduced into the stomach of a dog by way of a gastric fistula. In 1924, Vaughn and one of us (L. R. D.) found that the legs of living frogs would be similarly digested away if immersed in test tubes containing pure gastric juice obtained from a Pavlov pouch in a dog. In some recent unpublished experiments, Matthews and one of us (L. R. D.) determined that this digestion is proportional to the concentration of free hydrochloric acid in the gastric juice and is little affected by the concentration of active pepsin. Thus, when the concentration of free hydrochloric acid in the juice was reduced below 0.15 per cent, no digestion of the exposed leg occurred, even though the pepsin concentration was 600 units. Conversely, vigorous digestion took place with a gastric juice of 0.45 per cent hydrochloric acid and only 20 units of pepsin.

The assumption that active pancreatic juice can digest living tissues finds its best support in the common observation that the discharges from high intestinal fistula usually cause extensive corrosion of the surrounding skin. Rosenbach (1911) reported hemorrhages in the tongue of a frog produced by the local injection of a solution containing apparently some active trypsin. The discovery that active pepsin was innocuous to living tissue suggested that a similar trial be made with trypsin. To our considerable surprise, however, the highly proteolytic pancreatic juice obtained from a fistula as illustrated in figure 1 had no digestant effect on the legs of living frogs. In a series of experiments, the hindlegs of living frogs were immersed in dog pancreatic juice containing a trypsin concentration in some cases as high as 1,000 units per cubic centimeter for as long as twenty-four hours without showing any gross evidence of digestion. Control experiments with pure gastric juice under the same conditions produced complete digestion of the skin and underlying muscles in from four to six hours. It would appear that active trypsin is just as powerless to attack living tissue as is active

pepsin, and, furthermore, that the amount of free alkali in pancreatic juice is far less corrosive than is the concentration of free hydrochloric acid in pure gastric juice.

It is clear that these experiments yield data concerning the resistance only of skin, fascia and muscle to the digestant action of active trypsin. In the following experiments an attempt was made to determine the resistance of the pancreas itself to such digestion. In 1924, Vaughn and one of us (L. R. D.) studied the resistance of various tissues to gastric digestion by implanting such organs as the spleen, kidney and intestinal mucosa into artificial defects made in the wall of the stomach in dogs. They observed that so long as the blood supply of the implant remained normal it was not digested away by the gastric content. In the present experiments, operations were performed on large, healthy dogs under general anesthesia and with strict aseptic precautions. A window approximately 2 by 5 cm. was made in the anterior wall of the duodenum about 5 cm. distal to the entrance of the lower pancreatic duct. The portion of the pancreas lying free in the adjacent duodenal mesentery was then carefully turned over and stitched into the defect in the duodenum (fig. 2). Great care was observed not to interfere with the blood supply to the pancreas in any of the manipulations. The procedure was by no means as difficult as anticipated. Pancreatic juice entering the duodenum and becoming activated on passing over the duodenal mucosa had then free access to the pancreas implant. It was appreciated, of course, that the capsule of the pancreas rather than the parenchyma would first come into contact with the active trypsin. When it was shortly found that this did not result in necrosis or digestion of the exposed pancreas, similar implants from which the capsule had been first removed and the parenchyma bared by deep grooves were exposed to the digestant action of the duodenal secretions. In neither case did digestion of the pancreas occur, although it was left exposed for periods of from several days to three months. In the latter case the duodenal mucosa had regenerated and more or less completely covered the defect. In three experiments the pancreas was implanted into a window made in the anterior wall of the stomach. The results here substantiate those found by Vaughn and one of us (L. R. D.) with the spleen and kidney. The exposed pancreatic parenchyma was not digested away by the gastric content. Microscopic sections displaying areas of the pancreas exposed to the digestant action of duodenal and gastric content respectively are shown in figures 3, 4, 5 and 6.

It seems clear that in the dog at least the active proteolytic enzymes present in the gastric or duodenal content are entirely unable to bring about necrosis or digestion of the living pancreas. A duplication of this experimental procedure is not infrequently observed in man when the floor of a large perforating gastric or duodenal ulcer is found to

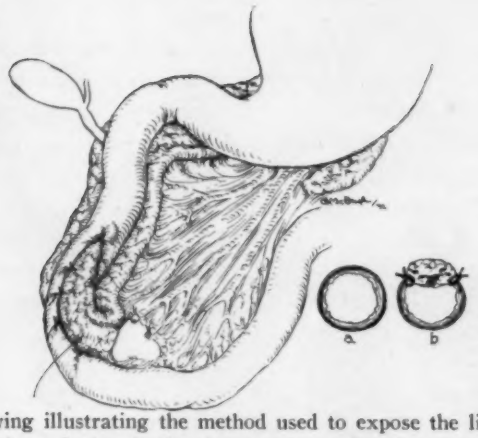

Fig. 2.—Drawing illustrating the method used to expose the living pancreas to the digestant action of the duodenal content; *a* shows a cross-section of the duodenum and *b*, a cross-section of the incised duodenum with pancreatic implant.

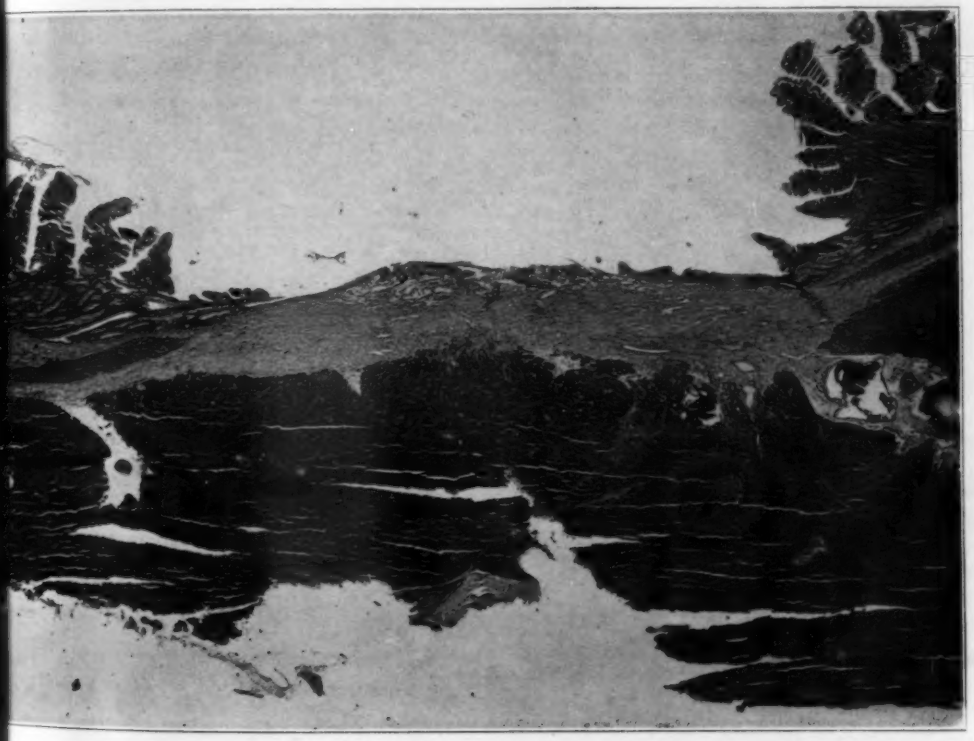

Fig. 3 (dog 272).—Section showing the pancreas implant in a window made in the anterior wall of the duodenum. Although exposed to the duodenal contents for eight days, there has been no digestion or evidence of necrosis of the pancreas. Regenerating duodenal epithelium may be seen extending from each side and partially covering the pancreas.

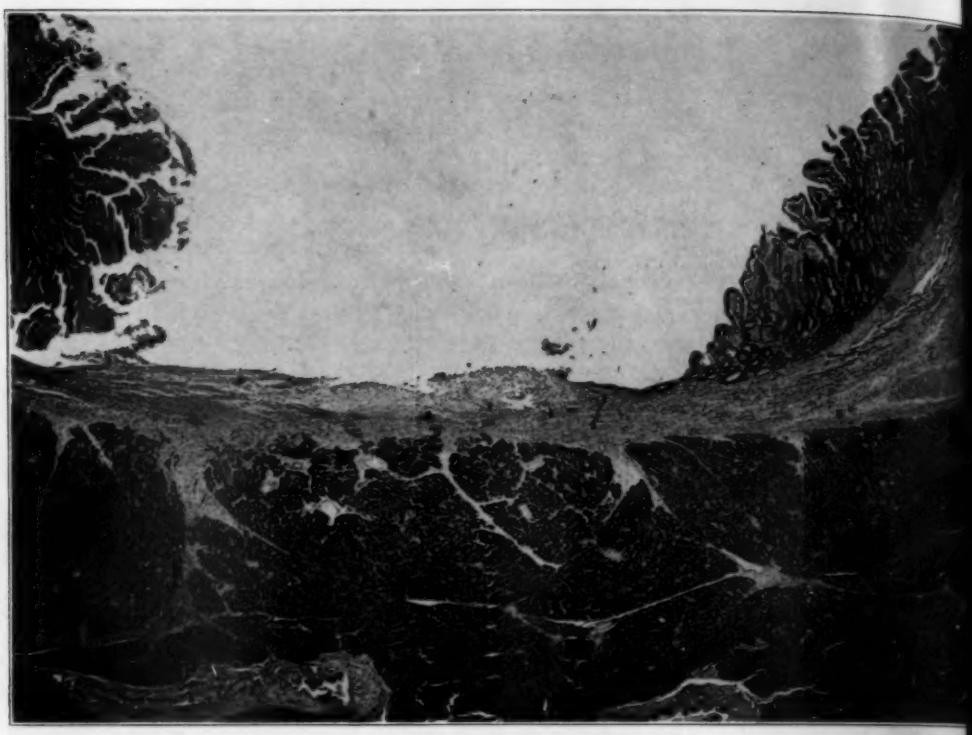

Fig. 4 (dog 108).—Section showing the pancreas implant in a window made in the anterior wall of the duodenum. Although exposed to the duodenal content for seven days there has been no digestion or evidence of necrosis of the pancreas.

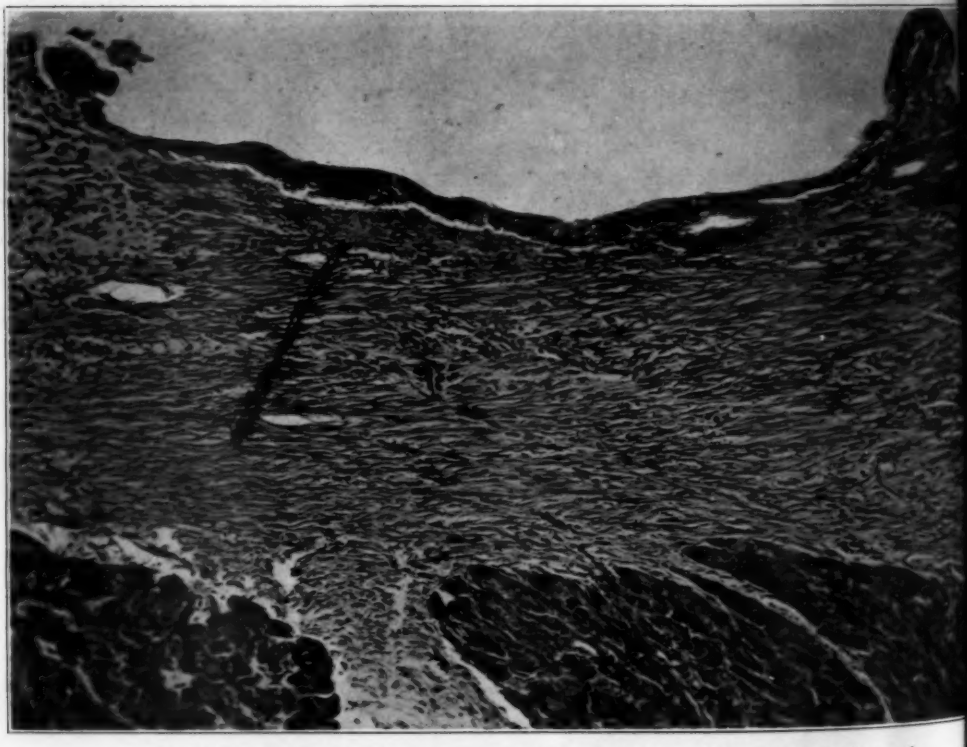

Fig. 5 (dog 108).—High power magnification of the section shown in figure 4. The regenerating duodenal epithelium is clearly seen, as well as the absence of evidence of digestion or necrosis of the pancreas implant.

consist partly or entirely of the pancreas. In the great majority of these cases digestion and necrosis of the exposed pancreas have not occurred. Exceptional instances in which an acute pancreatic necrosis has arisen as a result of a perforating gastric or duodenal ulcer have been reported by Bartels (1909) and Brocq (1919). Pearce (1904) reported a case in which a sinus from the stomach permitted intimate contact of the gastric juice with the pancreatic parenchyma, but it failed to cause acute pancreatitis.

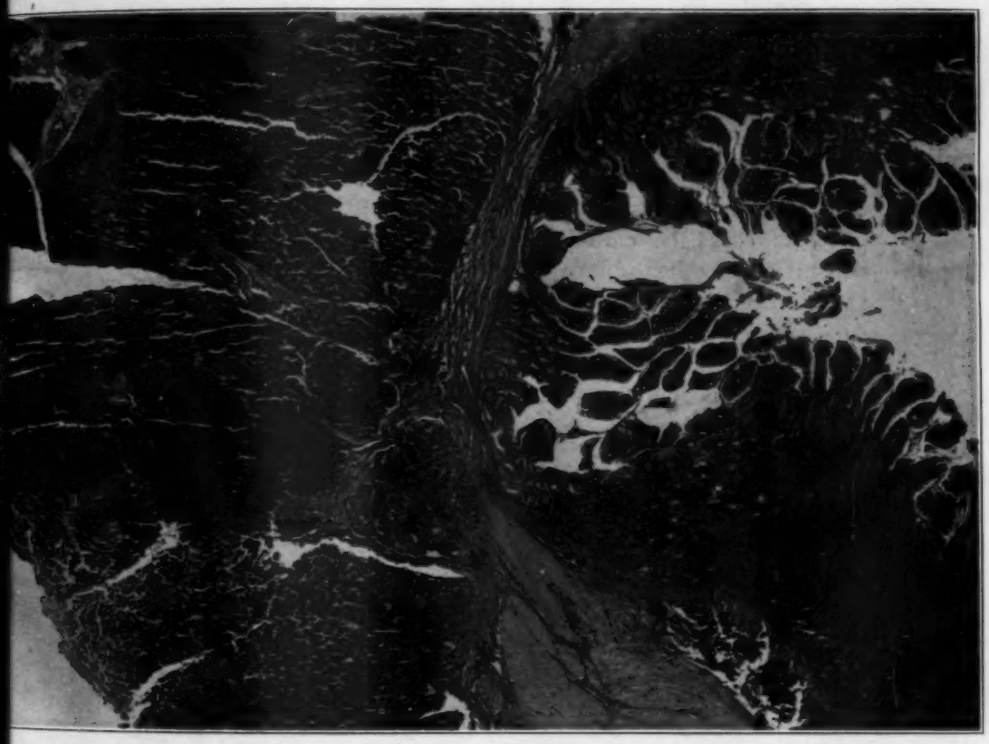

Fig. 6 (dog 734).—Section showing the pancreas implant in a window made in the anterior wall of the stomach. Although exposed to the gastric content for forty days, there has been no evidence of digestion or necrosis of the pancreas. The regenerating gastric mucosa has completely covered the implant.

The experiments with the pancreas implants in the duodenum and stomach and the instances in which a perforating ulcer has laid bare the underlying pancreas are subject to the criticism that in these cases the pancreas has been exposed, not to pure active pancreatic juice, but to the gastric or duodenal content. In the latter case it is likely that the alkalinity of the pancreatic juice has been partially reduced or neutralized by the acid of the gastric secretion and the activity of the tryptic

proteinase reduced by the accumulation of end-products of tryptic digestion. That this criticism is valid was recently illustrated in some unpublished experiments of Matthews and one of us (L. R. D.). Organs such as the spleen and kidney, which are unaffected by exposure to the gastric content, are digested away if implanted in the wall of a large Pavlov pouch, where they come into contact with pure gastric juice. In the following experiments an attempt was made to determine the effect of exposing the living pancreas of a dog to the digestant action of pure activated pancreatic juice. Animals were anesthetized by the oral administration of barbital, and the pancreas was exposed by a right rectus incision. The portion of the pancreas lying free in the duodenal mesentery was isolated by ligating and dividing a few small veins. Pure active pancreatic juice was secured from a fistula in a dog as illustrated in figure 1. About 50 cc. of this highly proteolytic secretion was placed in a small beaker, and this was then introduced into the abdominal cavity in such a way that the isolated portion of the pancreas could be entirely immersed in the pancreatic juice. The omentum and other viscera around the beaker kept the pancreatic juice at approximately body temperature. Three experiments of this type were performed. The animals were kept under complete anesthesia on the operating table until the conclusion of the experiment, when they were killed. Although continuously bathed in pancreatic juice for five, six and seven hours, respectively, in no case did the exposed area of pancreas show any evidence of digestion or necrosis in either gross or microscopic examination. These are short periods no doubt, but if the juice were markedly destructive, it would seem probable that some evidence should appear in this time.

We are well aware that in all of these trials the outer portion of the pancreatic acinus was exposed to tryptic digestion, whereas the theory postulates that it is the pancreatic juice within the ducts that, on activation, attacks the parenchyma. It is difficult to see how this could make any material difference. Many investigators have studied the effect of active trypsin within the pancreatic ducts either by the intraductal injection of active pancreatic juice, active trypsin solutions or substances such as succus entericus which have the property of activating trypsinogen. Roger and Garnier (1905, 1910), Falloise (1905), Carnot (1908) and Polya (1912) reported that the injection of active pancreatic juice into the pancreatic ducts of dogs produced a fatal pancreatic necrosis. According to Polya, active trypsin (a commercial preparation) was more effective in producing such necrosis than any other substance tried. When inactivated by heat, it was without effect. Williams and Busch (1907) and Mann and Giordano (1923) criticized many of these experiments on the basis that the amount of fluid injected was usually so large as to distend the finer ducts to the point of rupture

or to injure the tissue from simple mechanical distention. In an attempt to control this point, we made experiments with 3 healthy dogs each weighing approximately 7 Kg. The lower pancreatic duct in each case was isolated, and 3 cc. of active pancreatic juice obtained from a fistula, as illustrated in figure 1, was injected into the duct toward the gland and the duct subsequently severed from the duodenum and ligated. The juice used was previously determined to have a trypsin concentration of approximately 1,000 units per cubic centimeter. Studies were made of the nonprotein nitrogen, sugar and chlorides of the blood both before and after the injections. During the first twenty-four hours, the animals were considerably depressed, but no vomiting occurred. They soon regained their normal state. There were no significant alterations in the blood chemistry. All the dogs were electrocuted after fifteen days and the pancreases carefully examined. No gross or microscopic evidence of pancreatitis and no areas of fat necrosis were found.

The literature dealing with attempts to produce acute pancreatitis by the injection of substances that might be expected to activate intraglandular trypsinogen is conflicting, and no one seems to have been very successful in producing such an acute necrosis. Eppinger (1905-1906) and Polya (1906) reported a few rather inconclusive experiments. Williams and Busch (1907) injected from 0.5 to 8 cc. of duodenal contents into the pancreatic ducts of dogs and cats. Acute pancreatitis developed in 30 per cent of these, the outcome in 2 cases being fatal. They concluded that the large amount of fluid injected ruptured the finer pancreatic ducts, for in control experiments in which similar amounts of fluid containing lampblack were injected, some of the particles were found free in the tissues. They then prepared emulsions of duodenal mucosa, sterilized by Berkefeld filtration, and injected small amounts (from 2 to 2.5 cc.) into the pancreatic ducts of 6 cats at the height of digestion, with no cases of acute pancreatitis resulting. Starling (quoted by Eve, 1915) similarly failed to produce acute pancreatitis by injecting succus entericus, sterilized by Berkefeld filtration, into the pancreatic ducts of dogs. Seemingly at variance with this experience in the laboratory have been the cases of acute pancreatitis in man in which the necrosis was limited to the portions of the gland drained by the duct of Santorini (Bassett, 1907; Johnstone, 1907; Opie and Meakins, 1909, and Simkins, 1931). These observations suggest that the etiologic agent was some material (duodenal contents) introduced into the gland via the duct. In the same category belong those cases in which an acute pancreatitis followed wide dilatation of the ducts in sloughing carcinoma of the ampulla or in which an Ascaris was found in the duct entrance (von Schmieden and Sebening, 1927). Grant (1928) called attention to the fact that the entrance of the duct of

Santorini is not protected by a sphincter, and suggested that violent vomiting may force succus entericus from the duodenum into the duct. This seems improbable since in that case we should have to assume that the general increase in intra-abdominal pressure during vomiting would be transmitted to the duodenum and not to the equally distensible pancreatic ducts. The motility of the duodenum itself is probably more effective. In this connection it should be recalled that Pearce (1904) demonstrated long ago that under normal conditions it is practically impossible to force colored liquids from the intestine of the dog into the bile or pancreatic ducts. Seidel (1910) produced a closed segment of the first part of the duodenum (the portion receiving the ducts) in dogs, and stated that the animals died in forty-eight hours with extreme hemorrhagic necrosis of the pancreas, presumably as a result of the entrance of material from the loop into the pancreatic ducts. It should be noted, however, that the production of a similar closed segment of the duodenum below the ducts will also cause death in forty-eight hours with extreme splanchnic engorgement (Whipple, Stone and Bernheim, 1913; Moorhead, Burcky and one of us [L. R. D.] 1917), and it seems probable to us that Seidel has confused this picture with acute pancreatitis. Wilkie (1921) reported a case of acute pancreatitis in a patient with duodenal dilatation, and Duval, Roux and Béclère (1928) emphasized the possibility of duodenal stasis causing a regurgitation into the duct of Santorini. Robson (1904) recognized long ago the potential danger of the damming back of infected pancreatic juice as a result of obstruction by a stone in the ampulla, a view elaborated by Nordmann (1913). Indeed, we may probably correctly assume that stasis of pancreatic juice within the dilated ducts from obstruction of any cause would in some instances be shortly followed by proliferation of bacteria in the stagnant secretion. Intestinal bacteria grow readily in pure pancreatic juice. The increased pressure within the ducts due to continued secretion and bacterial growth might well injure the walls of the duct by distention, a condition no doubt aggravated by the local toxic action of the bacteria or their products. Eve (1915) suggested that the bacteria play a double rôle: They injure the pancreatic cells by their toxins, and by their proteolytic ferments they activate the pancreatic juice, which in turn digests the damaged tissue. He quoted H. M. Vernon to the effect that various intestinal bacteria, particularly B. coli, secrete powerful proteolytic ferments which can activate trypsinogen entirely independent of enterokinase, a view shared by Mellanby and Quolley. In most cases, however, a stagnation of pancreatic juice within the ducts as a result of ligature or other obstruction produces only a gradual atrophy of the parenchyma leaving the islet tissue intact.

MECHANISM OF PRODUCTION OF PANCREATIC NECROSIS BY BILE

Claude Bernard (1856) is usually credited with being the first to produce acute pancreatitis by the injection of bile. He introduced a mixture of one part of olive oil to two parts of bile into the larger pancreatic duct of a dog and undoubtedly secured a typical and fatal pancreatitis. Subsequent work by a great number of investigators demonstrated that the injection of 5 cc. or more of gallbladder bile into the pancreatic duct and subsequent ligation will produce a fatal pancreatitic necrosis in the majority of instances (Opie, 1901; Flexner and Pearce, 1901; Hewlett, 1904; Guleke, 1904; Polya, 1912, and Nordmann, 1913). The often repeated suggestion that the bile activates the trypsinogen in the duct system of the pancreas and causes necrosis in this way is probably erroneous. There is little conclusive evidence that bile activates trypsinogen, and there is no doubt about the fact that gallbladder bile produces acute pancreatitis with far greater regularity than succus entericus which contains enterokinase, the specific activator of the tryptic proteinase. It is more probable that the well known cytolytic and necrotizing properties of bile are directly responsible. It has been amply demonstrated that a wide variety of chemicals will produce pancreatic necrosis if injected into the ducts. For the most part, these have in common only the property of being locally destructive to protoplasm. The following substances have been tried and found effective: olive oil (from 5 to 8 cc.—Hess, 1903; Hewlett, 1904; Guleke, 1904, 1905, 1906, 1908; Eppinger, 1905), hydrochloric acid (5 cc. of 0.5 to 2 per cent solution—Flexner and Pearce, 1901; Hewlett, 1904), sulphuric acid (Flexner and Pearce, 1901), nitric acid (Flexner and Pearce, 1901), formaldehyde (Flexner and Pearce, 1901), zinc chloride (Lattes, 1913), chromic acid (Lattes, 1913) and calcium chloride (Binet and Brocq, 1920). It is probable that olive oil owes its activity to the liberation of highly irritating fatty acids and the formation of toxic soaps. Hess (1903) produced pancreatic necrosis by injecting from 5 to 7 cc. of oleic acid into the pancreatic ducts, and Trevor (1904) secured a similar result with a mixture of oleic acid and 4 per cent sodium soap solution. Sailer and Speese (1908) suggested that this great variety of substances that cause pancreatic necrosis on injection into the ducts is proof that it is mechanical distention of the pancreatic tissue that is the destructive agent. This objection does not appear to be valid in view of the many reports that the injection of equal amounts of bland substances does not produce necrosis. The following substances have been injected into the ducts without harmful effect: blood (Flexner and Pearce, 1901; Guleke, 1904-1908), blood serum (Flexner and Pearce, 1901), glycerin (Hess, 1903), paraffin (Hess, 1903), agar-agar (Lattes, 1913) and starch (Hess, 1903).

A fairly extensive literature exists with respect to the local and systemic toxic properties of bile and certain of its constituents. Rywosch (1901) seems to have been the first to demonstrate the toxic effect of bile on cells and its hemolyzing effect on red blood corpuscles. His results were confirmed by Flexner (1906), Meltzer and Salant (1906) and many others. Meltzer and Salant made detailed studies on the toxicity of bile and bile salts and listed an extensive bibliography. They appreciated the fact that bile salts would cause a local necrosis on contact with living cells. Bunting and Brown (1911) injected from 0.5 to 1 cc. of gallbladder bile into the peritoneal cavity of rabbits and found that the great majority died within eighteen hours. These findings were confirmed by Horrall (1929) on the dog. In one experiment we exposed the pancreas to direct contact with gallbladder bile by the following method: A dog was operated on under general anesthesia and with the usual aseptic precautions. A window was made in the gallbladder approximately 3 by 1.5 cm. in size, and the free portion of the pancreas was carefully stitched into the defect. The animal recovered from the immediate effects of the operation but died in depression fifty hours later. Autopsy disclosed an acute necrosis of the portion of the pancreas exposed to the bile. There was no evidence of peritonitis nor was there any bile in the peritoneal cavity. Flexner (1906) clearly demonstrated that the bile salts constitute the toxic element in bile and that the remaining fractions are not only not injurious but actually inhibit the destructive action of the salts. For this reason we should expect gallbladder bile, in which the bile salts are relatively concentrated, to be more toxic than hepatic duct bile. Most of the investigators previously mentioned produced pancreatic necrosis with gallbladder bile. Sodium taurocholate and sodium glycocholate are apparently equally toxic (Sellards, 1908). The suggestion of Tatum (1916) that the cytolytic action of bile is due to its activating the intracellular autolytic enzymes and that the process is essentially an autolysis of the cells was questioned by Bradley and Taylor (1917). The latter workers found that bile did not accelerate the autolysis of liver, spleen, kidney, thymus or heart muscle to any significant degree. They sharply distinguished between cytolysis and autolysis and concluded that bile does not activate the enzymes associated with autolysis. Andrews, Rewbridge and Hrdina (1931) recently confirmed the observations of Bunting and Brown (1911) and Horrall (1929) and, in addition, demonstrated that hemorrhagic peritonitis produced by the escape of bile or the injection of sterile bile salts into the peritoneal cavity is regularly associated with the invasion of B. welchii and similar organisms presumably from the intestinal tract. It is probable that the systemic intoxication in this so-called "bile peritonitis" is at least partly due to the toxins of B. welchii, although direct proof for

this statement is still lacking. In 1929, Spurrier and one of us (L. R. D.) demonstrated that bile alone can produce a fatal systemic intoxication. These investigators found that if the common bile duct of dogs was anastomosed to the vena cava or portal vein so that all of the bile passed directly back into the circulation, death regularly followed within two or three days. Sellards (1909) injected 3 cc. of a solution (2, 5 and 13 per cent strength) of sodium taurocholate into the ducts of the parotid and submaxillary glands and secured a fairly extensive necrosis of the secreting parenchyma. Andrews (1931) produced extensive necrosis of muscle and subcutaneous tissue by the injection of sterile bile or solutions of bile salts. We have confirmed the observations of Sellards and in addition have injected sterile gallbladder bile into the pelvis of the dog's kidney, followed by ligation of the ureter. In 3 healthy dogs bile was secured from the gallbladder, and 2, 6 and 8 cc., respectively, were injected into the right ureter toward the kidney. These animals were killed after twenty-four hours, and the kidneys examined both grossly and under the microscope. The pelvis of the kidney receiving 8 cc. of bile was filled with blood, and there were definite areas of necrosis and hemorrhage throughout the renal substance. The smaller amounts of bile produced mostly edema, round cell infiltration and a moderate amount of hemorrhage. In no case could the extent of the pathologic change be compared with that resulting from the injection of a like amount of bile into the pancreatic duct. Sellards (1909) similarly concluded that the lesions produced in the salivary glands by the injection of bile were less marked although similar in character to those developing in the pancreas.

There seems to be little doubt but that the pancreas is more susceptible to the local necrotizing effect of bile or bile salts than most other tissues, a conclusion voiced by Bunting and Brown (1911). It is probable that this increased susceptibility is in some way dependent on the fact that the pancreas manufactures such an active digestive secretion and one which can digest all three classes of food substances. It has been commonly remarked that acute pancreatitis is especially prone to occur immediately after a heavy meal. Many investigators have concluded that the incidence of fatal pancreatic necrosis following the intraductal injection of bile, bile salts or even other irritants is much increased if these injections are made during the height of digestion or when the pancreas has been excited by the injection of pilocarpine (Hess, 1903; Doberauer, 1906; Polya, 1912; Brocq and Morel, 1919; Wangensteen, Leven and Manson, 1931). These findings have led many naturally to conclude that the destructive agent is one of the enzymes (usually trypsin) manufactured during such periods of activity, a view we believe to be untenable. There is, however, evidence which indicates that the toxic effect of bile and perhaps of other chemicals is increased

by the presence of an active proteolytic agent. Flexner (1908) found that the mucus in bile, as well as certain other colloidal substances, limited the destructive effect of bile salts. He concluded that this was due to a lessening of the diffusibility of bile salts by the larger colloidal particles, an explanation suggested by Ostwald. Sellards (1908, 1909) reported that normal serum protects effectively against the hemolytic action of bile, a fact previously demonstrated by Bayer (1907). Bayer also showed that the inhibitory agent in the serum rests largely, if not entirely, in the protein constituents. Only the proteins of serum were found to be protective, edestin and egg albumin being without effect. Digestion of the serum by trypsin or pepsin completely destroys its protective capacity. Do we not have here a possible explanation for the extensive necrosis produced by the injection of bile into the ducts of the actively secreting pancreas? May we not assume that the initial attack of the bile has been repulsed by an exudate of serum or even frank hemorrhage? The protecting colloids being dead, proteins are then promptly digested by the tryptic proteinase and polypeptidase of the pancreatic juice and the bile salts freed for further destructive action.

SUMMARY

In considering the etiology of acute pancreatic necrosis, it should be kept in mind that it is by no means necessary to determine a single cause for all cases in order to satisfy the existing evidence with regard to its pathogenesis. Thus, the discovery of a case of acute pancreatitis in which the bile duct and pancreatic duct empty separately into the duodenum cannot be construed as evidence against the theory of Opie, but only that it is inadequate in the particular case, which may have been due to trauma, hematogenous, lymphogenous or ductal infection, or vascular injury. On the basis of the evidence existing at present, it seems probable to us that approximately 60 per cent of the cases of acute pancreatitis occurring in man have developed as a direct result of the passage of bile over into the pancreatic ducts. Included in this group are a majority of those in which an antecedent cholelithiasis and cholecystitis have existed. In making this statement, we realize that, according to the available statistical evidence, in only one sixth of this number has a common channel due to obstruction at the papilla of Vater by a gallstone been demonstrated. It is necessary, then, to believe that in the remaining five sixths of this group a common channel has been produced either by spasm of the sphincter of Oddi, transitory stone obstruction or edema of the muocsa at the papilla. No direct evidence exists to support this belief, and it does not seem likely that it will soon appear. Perhaps the most that can be said is that its possibility has been demonstrated by Archibald in experiments on lower animals, and the inescapable fact that it is easier to produce acute

pancreatic necrosis by the injection of bile into the pancreatic ducts than by any other method based on pathologic events likely to occur in man. Bile seems to produce its effect through the local toxic and cytolytic properties of the bile salts, and its action is greatly facilitated by the proteolytic enzymes of the pancreatic juice which digest and remove the protective proteins of the blood serum. Infected bile should be more effective than sterile bile, since the bacteria or their products may activate the trypsinogen. Gallbladder bile should be more effective than hepatic duct bile because of its greater concentration of bile salts.

Of the remaining 40 per cent of cases in which it seems that bile has played no rôle, we may list the following events as etiologic factors in the necrosis. They are given in the order of their probable occurrence as judged by clinical reports, namely: extension of infection via the lymphatics from an infected gallbladder or neighboring viscus, trauma, hematogenous infection as in mumps, stasis of pancreatic juice plus infection (Nordmann, 1913; Eve, 1915), reflux of duodenal content into the duct of Santorini or into the duct of Wirsung rendered patent by the entrance of an Ascaris (von Schmieden and Sebening) or because of destruction by a carcinoma, vascular injury as a result of thrombosis or embolism, and extension from a perforated ulcer. There is evidence indicating that these and perhaps other factors as well may produce an entirely typical necrosis and, as we shall see later, irrespective of the cause of the necrosis, the nature of the toxemia and death is probably the same.

CAUSE OF DEATH IN ACUTE PANCREATIC NECROSIS

The prevalent theories as to the cause of death in acute pancreatic necrosis uniformly assume that it is due to a toxemia in some way arising from the diseased pancreas. There is little direct evidence, however, supporting such an assumption. Sailer and Speese (1908) secured some indication that the blood from the carotid artery of dogs with acute pancreatitis was more toxic for guinea-pigs than normal blood. Speese, Sailer and Torrey (1911) found an increased globulin content of the blood in experimental pancreatitis, and suggested that the globulin or some substance adherent to it constitutes the toxic element in the disease. During the past year, M. L. Montgomery and one of us L. R. D. (1931) demonstrated, by means of cross-circulation experiments, the exceedingly rapid removal of toxic chemicals from the circulating blood. It was found, for instance, that a double lethal dose of strychnine injected intravenously was so completely removed within three minutes that the blood from the animal into which the injection was made could be transfused into the circulation of a normal animal without producing any toxic effect. It follows, then, that a failure to demonstrate toxic effects on transfusion of the blood from

an animal dying from acute pancreatic necrosis into a normal animal should not be construed as proof of the absence of a toxemia. It is unfortunate that there is no reliable way of determining the existence of a suspected toxemia, and in this case, as in many others, we must be provisionally content with more indirect evidence. This may be summarized as follows: A bacteremia has not been demonstrated in patients with acute pancreatic necrosis, and the clinical symptoms and findings are such as to suggest a toxemia rather than an infection. At death, a necrotic pancreas is found in the abdominal cavity. Extracts of such a pancreas have been shown to be exceedingly toxic if injected into the abdominal cavities or into the veins of experimental animals. Surgical attempts to provide an extra-abdominal escape for the products arising from the necrotic pancreas have produced results that are favorable within the limitations of the method, itself admittedly inadequate. Chemical examination of the blood has failed to show a departure from the normal of sufficient degree to account for the lethal issue.

If it is agreed that the cause of death is the systemic absorption of poisonous materials from the necrotic pancreas, and at present the weight of evidence certainly suggests this conclusion, we may perhaps profitably inquire further into the nature of these toxic substances and their mode of origin. Some questions which naturally arise are these: 1. Are the various constituents of the pancreatic juice toxic if absorbed from the peritoneal cavity? 2. Are the products of the autolysis or digestion of the pancreas by activated pancreatic juice the responsible toxic agents? 3. Are these poisonous substances bacterial toxins or toxic fractions resulting from the presence of bacteria in an extensive area of dead tissue?

OBSERVATIONS ON THE TOXICITY OF PANCREATIC JUICE

As noted in a preceding section, it has been repeatedly observed that pancreatic necrosis may occur shortly after a heavy meal at a time when presumably the pancreas is actively manufacturing its secretion. Similarly, injuries to the pancreas during digestion are apt to be more serious than during the fasting state. Attempts to induce acute necrosis by the injection of bile or other irritants into the pancreatic ducts are reported to be more successful if the gland has been previously stimulated either by taking of food or by the administration of drugs such as pilocarpine (Hess, 1903; Doberauer, 1906; Polya, 1912; Brocq and Morel, 1919; Wangensteen, Leven and Manson, 1931). These observations have usually been interpreted to indicate that the toxic agent in pancreatitis is manufactured with the pancreatic juice. Guleke (1905-1906) concluded that trypsin was the responsible toxic substance, a view shared by Sweet (1915) and many others.

The data on the toxicity of pure, or inactive, and of activated pancreatic juice are somewhat conflicting. Lattes (1913) cited the following experimenters as having demonstrated that the injection of pancreatic juice mixed with intestinal juice into a peritoneal cavity or into a vein produces a severe toxemia and death, while the injection of inactive pancreatic juice produces no such effect: Lombroso (1903), Roger and Garnier (1905, 1908), Falloise (1907), Cybulski and Tartschanow (1907), Fleig (1908), Seidel (1909) and Kircheim (1911). On the other hand, Schittenhelm and Weichardt (1911) and Stradiotti (1909) reported that the injection of large amounts of pancreatic juice either into a vein or into the abdominal cavity produced no ill effects. Lattes (1913) criticized the experiments of the latter authors in that the digestive activity of the juice was not carefully controlled. He secured juice from a cannula tied in the pancreatic duct of a dog. This was found to be without digestant effect on coagulated egg-white but had a moderate fat-splitting activity. The injection of from 7 to 103 cc. of this pure nonproteolytic juice into the abdominal cavities of dogs caused widespread fat necrosis but no toxemia, and the animals survived. Activated pancreatic juice was secured from a dog provided with a fistula of the Pavlov type, in which the duodenal mucosa containing the entrance of the lower pancreatic duct had been implanted in the skin of the abdominal wall. This juice was found to digest egg-white and to split neutral fat. The intraperitoneal injection of from 25 to 30 cc. of this secretion caused death in from nine to thirty hours (experiments on 4 dogs).

Flexner (1897) credited Senn with having been the first to demonstrate that the passage of fresh or inactive pancreatic juice (as from a cut gland) into the peritoneal cavity does not cause diffuse inflammation or marked toxemia. In 6 dogs, Lattes freed and cut the pancreatic duct, permitting the pancreatic juice to flow freely into the peritoneal cavity. He concluded that this was innocuous whether done during digestion or in the course of long periods of fasting and attributed the absence of toxicity to the lack of proteolytic activity of the fresh juice. Similar experiments in which from 5 to 20 cc. of intestinal juice was injected into the peritoneal cavity to activate the escaping pancreatic juice caused death in from ten to twenty-eight hours. The intestinal juice alone, in amounts of from 2 to 14 cc., was found to be nontoxic on intraperitoneal injection. The latter experiments are in harmony with an earlier observation of Guleke (1908), who established an intraperitoneal fistula of the pancreatic duct, securing active juice by excision of the duodenal papilla which remained attached to the duct. Death occurred six days later, at which time 400 cc. of clear bloody fluid was found in the abdomen together with numerous areas of fat necrosis. Sweet (1915) confirmed the findings of Lattes and Guleke,

and concluded that the intravenous injection of inactive pancreatic juice produced only slight transitory lowering of the blood pressure, whereas the injection of pancreatic juice plus succus entericus, either into the peritoneal cavity or into a vein, caused the typical symptoms of pancreatic poisoning and death. Peterson, Jobling and Eggstein (1916), on the other hand, concluded that the serum changes observed during acute experimental pancreatitis were those of an intoxication from protein split products rather than from pure tryptic ferment. There was no increase in serum protease, as would be expected from pure trypsin shock.

In view of the crucial importance of this question and the conflicting reports of various observers, we have performed a number of experiments chiefly with the view of determining, if possible, the toxicity of activated pancreatic juice. As previously noted, most investigators have agreed that the inactive juice as it exists in the duct system of the pancreas is nontoxic either on intravenous or on intraperitoneal injection. Our experiments on this point have been limited to the production of an intraperitoneal fistula of the pancreatic duct. In 5 dogs the lower or main pancreatic duct was carefully dissected free from its entrance in the duodenal wall, the duct sectioned and the duodenal end closed. In 3 cases a small ureteral catheter was tied into the proximal portion of the duct, and in each instance pancreatic juice was observed coming from the catheter. This secretion was allowed to flow freely into the peritoneal cavity in all 5 experiments and the abdomen was closed. No symptoms of toxemia appeared. The animals were subsequently killed at intervals varying from five to sixty days, and at autopsy there was surprisingly little evidence of pathologic change within the abdomen. A few small areas of fat necrosis were found in the region of the divided duct, and in 1 case, about 50 cc. of thin, turbid fluid in the peritoneal cavity. In this case the omentum was edematous and somewhat congested. These changes confirmed the previous observations of Lattes, and it seems fair to conclude, therefore, that the volume of inactive pancreatic juice which escapes from such a fistula in the dog is insufficient to produce toxemia when poured out into the peritoneal cavity. We have, of course, no check on the amount of juice secreted in these experiments, but in control experiments in which the catheter was led to the outside through a stab wound in the abdominal wall the volume obtained from the lower pancreatic duct of the dog varied from 80 to 350 cc. per twenty-four hours.

The more debated question is that with respect to the toxicity of pancreatic juice after the trypsinogen has been changed to the active trypsin. It should be recalled here that the so-called inactive pancreatic juice contains an active starch-splitting enzyme, amylopsin, and also an active lipase, steapsin. It seems somewhat surprising that the activation

of the third enzyme should convert a nontoxic fluid into one so poisonous that the intraperitoneal injection of only 25 cc. (Lattes) would produce a fatal toxemia. It may be argued, however, that trypsin attacks the protein of the cell, the basic substance of protoplasm, while the other enzymes affect only storage products such as glycogen and neutral fat. Or it may be that the reported toxicity of trypsin is independent of its catalytic action, and the mere activation of trypsinogen changes it to a general protoplasmic poison. These possibilities have seemed to us unlikely on theoretical grounds, and we have accordingly attempted to determine anew the toxicity of active (protein-digesting) pancreatic juice.

Under normal conditions, trypsinogen is activated through its contact with the succus entericus when the pancreatic juice flows over the duodenal mucosa. As previously noted, Lattes found that fresh succus entericus obtained from a Vella fistula was nontoxic on intraperitoneal injection in amounts of from 2 to 14 cc. This observation was confirmed in 1917 by Moorhead, Burcky and one of us (L. R. D.), who reported that the fresh secretions of the duodenum, jejunum and ileum, when freed from bacterial contamination, were nontoxic when allowed to drain freely into the peritoneal cavity. If, however, these secretions were kept free from preservatives and unheated, they rapidly became exceedingly toxic (Davis and Stone, 1917), presumably as a result of the accumulation of the end-products of bacterial metabolism. The necessity of determining the toxicity of mixtures of pancreatic juice and succus entericus in the complete absence of bacterial contamination was thus evident. An attempt was made to achieve this by a combination of the intraperitoneal fistula of the pancreatic duct as in Lattes' experiment and the method used by Moorhead, Burcky and one of us (L. R. D.) to test the toxicity of intestinal juice. Eight dogs were operated on in the following manner, strict aseptic precautions and general anesthesia being employed. At a point approximately 50 cm. distal to the pylorus, the jejunum was cut across in two places about 5 cm. apart. Care was taken to preserve the mesenteric blood supply to the short segment of intestine thus produced, and its mucosa was everted by a longitudinal incision along the antimesenteric border. The continuity of the intestine was reestablished by an anastomosis between the proximal and the distal jejunum. The abdomen was then closed, leaving the everted patch of jejunum to pour its secretions freely into the peritoneal cavity. One of the 8 dogs died of generalized peritonitis, but the remaining 7 showed no ill effect from the escape of succus entericus into the abdominal cavity. A second operation was done from two to three weeks later. At this time the lower pancreatic duct was isolated and cut, the duodenal end closed, and a catheter tied into the proximal end. The distal end of the catheter was sutured to the flap

of everted jejunal mucosa so that the outflowing pancreatic juice would pour over its surface and become activated before escaping into the peritoneal cavity (fig. 7). Of these 7 animals, 1 died from the anesthetic; 1 died from evisceration in sixty hours, and 3 died in twenty, forty-six and seventy hours, respectively, autopsy showing generalized peritonitis and extensive fat necrosis. In each of these cases bacteria (streptococci, staphhylococci and B. welchii) were obtained on culture from the jejunal patch at the time of the second operation and again at autopsy. Two animals survived the second operation and displayed no subsequent ill effects. These were killed twenty-eight days later. Autopsy revealed a small amount of turbid fluid in the abdomen (20 and

Fig. 7.—Drawing illustrating the intraperitoneal fistula of the pancreatic duct arranged so that the escaping fluid would come in contact with the mucosa of a sterile segment of the jejunum and become activated.

35 cc., respectively). The omentum was edematous and somewhat injected. No areas of fat necrosis were found. Cultures taken from the jejunal patch at the time of the second operation revealed the presence of B. welchii, streptococci and a small gram-negative bacillus.

It is difficult properly to evaluate these experiments. The three animals that died showed unmistakable evidence of a bacterial peritonitis, which might well have been the cause of death. In this case the pancreatic juice must have served as a contributing factor, since all the animals survived the production of the open section of jejunum, the source of infection. On the other hand, in the case of the 2 dogs that survived the second operation, we can hardly conclude that this proves

the nontoxicity of active pancreatic juice, since we do not know how much was poured out into the abdomen, nor have we any check on its digestive activity. In both cases pancreatic juice was observed coming from the catheter before the abdomen was closed, and it is possible that this secretion continued throughout the duration of the experiment. These strictures must apply to all similar experiments described in the literature.

In the following series of experiments active pancreatic juice was secured from the dog by means of the special type of pancreatic fistula illustrated in figure 1. The juice is, of course, activated by its contact with the duodenal mucosa lining the sac into which the cannula is fixed. Numerous determinations of the trypsin content of this product have been made by the method of Northrop and Hussey (1922-1923), and the results have shown a relatively uniform and exceedingly active secretion from day to day. With the unit of active trypsin defined by these workers, the concentration of active enzyme in 1 cc. of this pancreatic juice varies between 1,000 and 1,500 units. The activity rapidly decreases on standing at room temperature; less so if kept in the icebox. Passage through a Berkefeld filter reduces its trypsin content approximately 20 per cent. The sterile filtrate preserves its activity on standing much longer than the infected juice. The toxicity of this actively proteolytic pancreatic juice was determined by both intraperitoneal and intravenous injection into the dog and intraperitoneal injection into mice. Tests were made with the fresh juice obtained from the fistula and with the same material after filtration through a Berkefeld filter. Cultures were made to check the sterility of the filtrate. The experiments are described in the following protocols:

Intraperitoneal Injection of Fresh, Actively Proteolytic Pancreatic Juice.—Dog 306.—March 18, 1930: Fifty cubic centimeters of fresh, active pancreatic juice obtained from a pancreatic fistula and centrifugated to remove mucus and some cellular débris was injected into the peritoneal cavity. Vomiting occurred immediately. The dog was found dead twenty hours later. Autopsy revealed a small amount of bloody fluid in the abdomen, but no gross evidence of peritonitis and no fat necrosis.

Intravenous Injection of Fresh, Actively Proteolytic Pancreatic Juice.—Dog 307.—This animal weighed 12.4 Kg.; 1,070 cc. of pancreatic juice was collected from a special pancreatic fistula in twenty-four hours. The juice was centrifugated at high speed for fifteen minutes to remove suspended matter. Fifty cubic centimeters was injected intravenously. Defecation occurred immediately, and within an hour profuse salivation, vomiting and marked depression. The dog was found dead in the cage twenty hours after the injection. Autopsy revealed an extensive hemorrhagic injection of the mucosa of the duodenum, small intestine and colon. The small intestine was filled with blood and secretion.

Dog 41.—This animal weighed 9.5 Kg. One hundred cubic centimeters of fresh, active pancreatic juice from which the suspended matter had been removed by centrifugation at high speed for fifteen minutes was injected intravenously.

There was immediate defecation. In an hour a profuse bloody diarrhea developed, and the animal became markedly depressed. Death occurred four hours after the injection. There was an extensive hemorrhagic injection of the mucosa of the duodenum, small intestine and colon, and the intestines were filled with bloody mucus. Numerous small white areas were found in the pancreas. These grossly resembled areas of fat necrosis.

Intraperitoneal Injection of Fresh, Actively Proteolytic Pancreatic Juice, Sterilized by Berkefeld Filtration.—Dog 102.—Aug. 26, 1930: This animal weighed 10.6 Kg. Seventeen cubic centimeters of active pancreatic juice was collected from the fistula, immediately passed through a Berkefeld filter, and the filtrate injected into the peritoneal cavity. Cultures of the filtrate on blood agar plates, dextrose broth and litmus milk remained sterile. The milk was markedly digested by 1 drop of the juice. The dog evinced discomfort for several minutes after the injection but soon became quiet and displayed no subsequent ill effects. August 28: The dog apparently was normal. Twenty cubic centimeters of a Berkefeld filtrate of fresh, active pancreatic juice was injected into the peritoneal cavity. Cultures of the filtrate on blood agar plates and dextrose broth showed a small gram-negative bacillus. Litmus milk was markedly digested by 1 drop of the filtrate. Immediately after the injection, the dog showed discomfort and vomited repeatedly. Recovery apparently was complete. August 30: The dog apparently was normal. Thirty cubic centimeters of a Berkefeld filtrate of fresh, active pancreatic juice, collected immediately before, was injected into the peritoneal cavity. Cultures of the filtrate remained sterile. Milk was markedly digested by 1 drop of the filtrate. The animal showed signs of pain as before and vomited, but later completely recovered. September 5: The animal apparently was normal. Twenty cubic centimeters of a Berkefeld filtrate of fresh, active pancreatic juice, collected immediately before, was injected into the peritoneal cavity. Cultures of the filtrate remained sterile. Litmus milk was markedly digested by 1 drop of the filtrate. The animal displayed little or no discomfort following the injection and remained in good condition. September 8: The animal was normal. Fresh, active pancreatic juice was collected and immediately passed through a Berkefeld filter. Cultures of the filtrate remained sterile. One drop of the filtrate produced marked digestion in milk. Fifty-five cubic centimeters of the filtrate was injected into the peritoneal cavity. There was slight evidence of pain with a moderate amount of vomiting ten minutes after the injection. Complete recovery followed. September 9: The animal apparently was normal. It was electrocuted. Autopsy revealed 20 cc. of turbid fluid in the abdominal cavity, no evidence of fat necrosis, normal omentum and a peritoneum that was smooth and shining. Cultures of the peritoneal fluid remained sterile.

In this experiment a total of 142 cc. of sterile pancreatic juice, proved by its digestion of milk to be actively proteolytic, was injected into the peritoneal cavity without producing toxemia or any marked amount of fat necrosis. The last two injections seemed to produce less peritoneal irritation than those preceding. Estimations of the blood chemistry showed: on August 26, chlorides, 287; nonprotein nitrogen, 24; sugar, 108 mg.; on August 28, chlorides, 318; nonprotein nitrogen, 29; sugar, 83 mg.; on September 9, chlorides, 319; nonprotein nitrogen, 34; sugar, 132 mg. It is not probable that these variations are significant.

Dog 62.—Aug. 26, 1930: This animal weighed 9.6 Kg. Active pancreatic juice was collected, stored in the refrigerator for twelve hours, and then passed through a Berkefeld filter. Cultures of the filtrate remained sterile, and 1 drop produced marked digestion of litmus milk. Twenty-five cubic centimeters of the filtrate was injected into the peritoneal cavity. The animal was temporarily

uncomfortable but showed no subsequent ill effects. August 28: The animal was normal. Fresh, active pancreatic juice was collected and immediately passed through a Berkefeld filter. Cultures of the filtrate revealed pure growth of a small gram-negative bacillus, and 1 drop caused marked digestion of milk. Twenty-five cubic centimeters of the filtrate was injected into the peritoneal cavity. The dog vomited once ten minutes after the injection, but showed no other adverse symptoms. August 30: The animal was normal. Thirty cubic centimeters of a Berkefeld filtrate of pancreatic juice which had been proved to be sterile and actively proteolytic as in previous experiments was injected into the peritoneal cavity. The dog vomited repeatedly for thirty minutes, then recovered and remained normal. September 5: The animal was normal. Twenty cubic centimeters of a Berkefeld filtrate of fresh pancreatic juice, which had been proved to be sterile and actively proteolytic was injected into the peritoneal cavity. The dog showed little or no discomfort from the injection, did not vomit, and remained normal. September 8: The animal was normal. Forty cubic centimeters of a Berkefeld filtrate of fresh pancreatic juice which had been proved to be sterile and actively proteolytic was injected into the peritoneal cavity. The dog vomited several times and showed signs of moderate discomfort, but in twenty minutes appeared entirely normal. September 9: The animal apparently was normal. It was electrocuted. Autopsy showed within the peritoneal cavity about 100 cc. of turbid, blood-tinged fluid in which were numerous globules of fat. The omentum was edematous and slightly hemorrhagic, and careful inspection revealed numerous minute speckled areas. These areas were also observed over the small intestine and colon. The pancreas was congested and was quite firm. Cultures from the peritoneal fluid revealed an anaerobic, gas-forming, gram-positive bacillus.

In this experiment a total of 140 cc. of sterile, actively proteolytic pancreatic juice was injected into the peritoneal cavity without causing any definite evidence of toxemia. There was, however, a much greater peritoneal reaction than in the preceding experiment. The isolation of a gram-positive anaerobic bacillus from the peritoneal exudate is interesting in view of the sterility of the juice injected, except for one case in which a small gram-negative bacillus was obtained on culture. In this connection it may be recalled that Andrews and Rewbridge demonstrated the production of severe peritonitis by the intraperitoneal injection of sterile bile or sterile bile salts. At autopsy in these cases a pure culture of B. welchii was repeatedly obtained. In this experiment also the later injections of pancreatic juice produced less of peritoneal symptoms (pain and vomiting) than those preceding. Studies on the blood chemistry yielded the following results: on August 26, chlorides, 290; nonprotein nitrogen, 30; sugar, 105; on August 28, chlorides, 324; nonprotein nitrogen, 33; sugar 96; on September 9, chlorides, 303; nonprotein nitrogen, 35; sugar, 167 mg.

Dog 298.—Sept. 22, 1930: This animal weighed 8.3 Kg. Pancreatic juice was collected from the fistula and immediately passed through a Berkefeld filter. Cultures of the filter on blood agar plates, dextrose broth and a special meat medium for anaerobes gave no growth. One drop of the filtrate produced marked digestion of milk. One hundred and ten cubic centimeters of the filtrate was injected into the peritoneal cavity. The animal evinced discomfort for a few minutes after the injection, but rapidly recovered and showed no subsequent ill effects. He did not vomit. October 1: The animal apparently was normal. Eighty-five cubic centimeters of a Berkefeld filtrate of fresh pancreatic juice which had been proved to be sterile and actively proteolytic was injected into the peritoneal cavity. The dog did not vomit and apparently felt little pain. Complete recovery followed. October 3: The animal apparently was normal. It was electrocuted. Autopsy

revealed no free peritoneal fluid and no evidence of fat necrosis; the peritoneum everywhere was smooth and glistening; there was slight hyperemia of the pancreas. Determination of the blood chlorides and nonprotein nitrogen gave values within the normal range.

In this experiment large doses (85 and 110 cc.) of active pancreatic juice sterilized by Berkefeld filtration were absorbed from the peritoneal cavity without causing toxemia or fat necrosis.

Intraperitoneal Injection of Fresh, Actively Proteolytic Pancreatic Juice from the Dog into Mice.—For this experiment pancreatic juice was collected from a dog with the special pancreatic fistula previously referred to (fig. 1). The juice was used immediately after collection. In one series of mice it was injected just as it came from the fistula; in a second series, it was first centrifugated at high

TABLE 1.—*Effect of Intraperitoneal Injection of Active Pancreatic Juice (from the Dog) into Mice*

Mouse	Weight, Gm.	Material Injected	Amount		Effect
			Total, Cc.	Cc. per Gm.	
33	31.7	Fresh active pancreatic juice of dog	0.5	0.0157	Sick; recovery in 48 hrs.
4	19.4	Fresh active pancreatic juice of dog	0.6	0.0309	Dead in 2½ hrs.
66	21.8	Fresh active pancreatic juice of dog	1.2	0.0550	Dead in 1¼ hrs.
38	25.1	Fresh active pancreatic juice of dog	3.2	0.1275	Dead in 3 hrs.
41	30.2	Same as in previous experiments but centrifugated	0.5	0.0165	Sick; recovery in 48 hrs.
42	19.6	Same as in previous experiments but centrifugated	0.6	0.0306	Dead in 12 hrs.
56	26.6	Same as in previous experiments but centrifugated	1.6	0.0601	Dead in 2 hrs.
51	20.7	Same as in previous experiments but centrifugated	2.6	0.1256	Dead in 45 min.
29	36.0	Same, but passed through Berkefeld filter	0.55	0.0153	No ill effect from injection
63	31.7	Same, but passed through Berkefeld filter	1.0	0.0315	Slight depression; recovery in 1 hr.
30	20.8	Same, but passed through Berkefeld filter	1.2	0.0577	Slight depression; recovery in 1 hr.
64	26.2	Same, but passed through Berkefeld filter	3.3	0.1259	Moderate depression; recovery in 24 hrs.

speed for fifteen minutes, while in the third it was first passed through a Berkefeld filter. The data are shown in table 1. There was no difference between the centrifugated and uncentrifugated preparations. In both cases the intraperitoneal injection of as little as 0.03 cc. of juice per gram of body weight caused death. On the other hand, the Berkefeld filtrate was so little toxic that a dose four times as great produced few or no symptoms.

Comment.—The results of our experiments with respect to the toxicity of pure inactive pancreatic juice (intraductal juice) confirm those of others, and we may probably safely conclude that in the dog at least the escape of pancreatic juice from the severed duct does not produce marked toxemia and but little peritoneal reaction. The active lipase in this juice seems to be entirely unable to digest the lipoid envelop of living cells and produce necrosis. The areas of so-called

fat necrosis, so characteristic of acute pancreatitis, probably represent areas of devitalized or dead cells the fat of which on coming into contact with the steapsin of the pancreatic juice has been converted into glycerin and fatty acids, the latter combining with the ubiquitous calcium to form soap. Some such explanation seems necessary to account for the widely scattered areas of such necrosis and the intervening more accessible normal fatty tissue.

It should be emphasized that pancreatic juice obtained directly from the duct is usually sterile (Elman and McCaughan, 1927), whereas that activated by admixture with succus entericus contains the usual intestinal bacteria. The intravenous injection of this contaminated pancreatic juice was found to cause a violent toxemia, characterized by the same extreme splanchnic engorgement that is produced by the toxic proteose of Whipple, histamine or the toxic substances accumulating in isolated closed intestinal loops. On the other hand, when such activated pancreatic juice was freshly obtained from the dog and immediately passed through a Berkefeld N filter, as much as 110 cc. was injected into the peritoneal cavity of a dog weighing 8 Kg. without producing toxemia. Similar results were obtained in the experiments on mice. The contaminated pancreatic juice was found to be toxic, whereas after Berkefeld filtration, 3.3 cc. injected intraperitoneally produced only a moderate depression. Calculated by weight, this would correspond to a dose of 1,260 cc. for a dog weighing 10 Kg.

It is probable that the degree of insult to the pancreas capable of producing fatal pancreatitis causes also complete cessation of pancreatic secretion. It has been the experience of most physiologists that the pancreas is exceptionally sensitive to trauma and that even a slight disturbance may stop secretion for many hours. In assaying the part played by trypsin in the toxemia of acute pancreatic necrosis, therefore, we should probably limit ourselves to such amounts as might reasonably be presumed to exist both in the intraductal pancreatic juice and the secreting cells. We have no definite data with respect to the concentration of trypsin, or rather of its precursor, trypsinogen, in the secreting cells at any one moment, but we shall probably not err greatly if we assume it to be of the same order of magnitude as in the pancreatitic juice. The pancreas of a dog weighing from 10 to 15 Kg. weighs from 30 to 35 Gm., and its autolysis within the peritoneal cavity might be expected to liberate no more trypsin than is contained in an equal weight of active pancreatic juice. The probable presence of trypsin-inhibiting substances in the autolyzing pancreas should make this estimate quite liberal.

If these strictures are valid, we must conclude that neither trypsinogen nor trypsin represents the toxic agent in this disease. Attempts such as those of von Bergmann (1906), Joseph and Prigsheim (1913),

and Ohno (1923) to produce immunity or a therapeutic serum by the injection of purified trypsin solutions, we should expect to be futile.

OBSERVATIONS ON THE TOXICITY OF END-PRODUCTS OF PANCREAS DIGESTION AND AUTOLYSIS AND THE RÔLE OF BACTERIA IN THE TOXEMIA OF ACUTE PANCREATIC NECROSIS

One of the methods frequently employed to study the toxemia of acute pancreatitis has been to remove the pancreas from one animal under strict aseptic conditions and implant it in the abdominal cavity of a second, where it is permitted to undergo self-digestion, or autolysis. Guleke (1904, 1905 and 1906) reported that when this is done profound toxemia develops in the animal receiving the pancreas implant, and death occurs in from nine to eighteen hours, a finding confirmed by many others (Maragliano, 1912; Lattes, 1913; Sweet, 1915). Death has usually been attributed to the assumed toxic properties of the pancreatic ferments or to various protein split products arising as a result of the autolysis of the gland. The successful production of a typical fatal toxemia when all extraneous bacterial contamination has been avoided has led practically all investigators to disregard the possibility of bacterial products playing a part in the disease.

A series of experiments performed by the senior author (L. R. D.) over a number of years on the nature of the toxemia in acute intestinal obstruction has led him to question seriously the probability of highly toxic products arising in the body as a result of the autolytic destruction of body protein in the absence of bacteria. It should be recalled that such autolysis is a normal physiologic process for removing dead cells and protein exudates, and that a mechanism exists for the utilization of its end-products in the metabolism of the organism. It is a common observation in pathologic processes that extensive areas of spleen, kidney, bone or muscle may undergo aseptic necrosis as a result of infarction without the production of a severe toxemia. It is possible in the dog to occlude the blood supply to the spleen, kidney or a short isolated segment of intestine, previously sterilized by prolonged drainage into the peritoneal cavity, without the development of adverse symptoms, provided bacteria do not gain access to the necrotic autolyzing tissue. In 1924, Mason, Davidson, Matthew and Rastello reported that the aseptic autolysis of portions of dog liver implanted in the abdominal cavity regularly produced a fatal toxemia. In these experiments the authors took pains to avoid bacterial contamination during the operations, but did not apparently make cultures of the normal tissue. This apparent exception led two of us to reinvestigate the question (J. C. E. and L. R. D., 1930). It was soon found that the uncontaminated hepatic tissues of normal dogs regularly contain bacteria (predomi-

nantly anaerobes resembling if not identical with B. welchii), and that the toxemia resulting from the in vivo autolysis of liver (as in the experiments of Mason and co-workers) is entirely dependent on the presence of these organisms. Presumably various highly toxic chemical fractions arise as a result of the activity of bacteria growing in a large area of dead and disintegrating tissue. These observations were soon confirmed by Dvorak (1932).

It seemed therefore advisable to determine in a similar way if bacteria are commonly present in the pancreatic tissues of healthy animals, and, if so, their relation to the toxemia resulting from autolysis of the pancreas in vivo. It seems strange, in view of the extensive bacteriologic studies of diseased tissues, that so little work has been done to determine the bacterial flora of normal organs or rather of the uncontaminated tissues of healthy living animals and man. In 1930, the

TABLE 2.—*Incidence of Bacteria in Uncontaminated Pancreatic Tissues of Healthy Living Rabbits* *

Rabbit	Smears	Blood-Agar Plates	Lactic Acid Medium	Milk Medium
1	Gram-negative bacilli	Gram-negative bacilli	B. coli	No growth
2	Gram-negative bacilli	Gram-negative bacilli	B. coli	No growth
3	Gram-negative bacilli	Gram-negative bacilli	B. coli	No growth
4	Gram-negative bacilli	Gram-negative bacilli	B. coli	No growth
5	Gram-positive bacilli	No growth	.....	Anaerobic bacillus
6	Gram-positive bacilli	Gram-negative bacilli	B. coli	No growth
7	Gram-positive bacilli	Gram-negative bacilli	B. coli	No growth
8	Gram-negative bacilli, gram-positive cocci	Staph. aureus	B. coli	No growth
9	Gram-positive bacilli	No growth	.....	Anaerobic bacillus
10	Gram-negative diplococci	Staph. albus	.....	Anaerobic bacillus

* The rabbits were anesthetized with ether. The abdomen was shaved and painted twice with tincture of iodine. Linen, gowns, rubber gloves and instruments were sterilized after each operation.

literature was briefly reviewed by two of us (J. C. E. and L. R. D.). The present experiments, decidedly limited in scope, have been performed merely to determine the presence of bacteria in the uncontaminated pancreatic tissues of living healthy rabbits and dogs. It is obvious that a more quantitative study is necessary as well as a more detailed investigation regarding the location of organisms in the pancreas and the relative frequency of different bacterial types. A summary of the results obtained to date is given in tables 2 and 3. It proves to our mind conclusively that bacteria are present in the pancreatic tissues of the great majority of healthy living rabbits and dogs.

The great importance of these bacteria in the toxemia resulting from in vivo autolysis of pancreas is demonstrated in the following experiments:

In Vivo Autolysis of Dog Pancreas Complicated by the Presence of Bacteria Commonly Found in the Uncontaminated Gland.—The data included in table 3 summarize the experiments with 18 dogs in which

a portion or the whole of the pancreas of a second animal has been secured with strict aseptic precautions and implanted into the abdominal cavity. Of these, 8 received one half of the pancreas from an animal

TABLE 3.—*Incidence of Bacteria in Uncontaminated Pancreatic Tissues of Healthy Living Dogs and the Relation of Bacteria to the Toxemia Arising from in Vivo Autolysis of Pancreas*

Dog	Amount of Pancreas Implanted	Cultures of Pancreas Before Implantation	Weight of Dog Receiving Implant, Kg.	Result of Implantation with Cultures of Peritoneal Exudate
986	½ of a pancreas; weight, 12 Gm. (wrapped in omentum)	Bacteria present but not identified	12.15	Dead 30 hrs.; B. welchii, streptococci and staphylococci
948	½ of a pancreas; weight, 16 Gm.	Staphylococci	6.5	Dead in 3 days; no cultures taken
949	½ of a pancreas; weight, 16 Gm.	Staphylococci	7.4	Survived; killed after 3 days; cultures lost
309	½ of a pancreas; weight, 20 Gm.	Gram-negative bipolar bacillus	6.5	Survived; killed in 11 days; staphylococci
916	½ of a pancreas; weight, 20 Gm.	Gram-negative bipolar bacillus	7.4	Survived; killed after 41 days; exudate sterile
275	½ of a pancreas; weight, 15 Gm.; cut in many fine pieces	No growth	7.7	Survived; killed after 14 days; peritoneal cavity sterile
276	½ of a pancreas; weight, 16 Gm.; cut in many fine pieces	No growth	6.4	Survived; killed after 14 days; peritoneal cavity sterile
983	½ of a pancreas; weight, 20 Gm.; triturated with 50 cc. sterile saline	Bacteria present but not identified	11.3	Survived; killed after 23 days; cultures of peritoneum revealed gram-positive bacillus and staphylococci
513	Entire pancreas; weight, 35 Gm.	No cultures taken	6.5	Dead in 18 hrs.; B. welchii in exudate
732	Entire pancreas; weight, 38 Gm.	Gram-positive anaerobic bacilli	7.5	Dead in 18 hrs.; B. welchii and gram-negative diplococci
629	Entire pancreas; weight, 34 Gm.	Gram-positive anaerobic bacilli	5.3	Dead in 24 hrs.; B. welchii and gram-positive diplococci
419	Entire pancreas; weight, 31 Gm.	Gram-positive and gram-negative anaerobic bacilli	6.0	Dead in 24 hrs.; B. welchii, streptococci, gram-negative bacilli
588	Entire pancreas; weight, 35 Gm.	Gram-positive anaerobic bacilli	6.4	Dead in 46 hrs.; B. welchii and staphylococci
636	Entire pancreas; weight, 35 Gm.	Gram-positive anaerobic bacilli	7.5	Dead in 22 hrs.; B. welchii, B. coli and staphylococci
788	Entire pancreas; weight, 30 Gm.	All cultures remained sterile	5.6	Dead in 20 hrs.; B. welchii
548	Entire pancreas; weight, 35 Gm.	All cultures remained sterile	12.0	Survived; killed after 21 days; peritoneal cavity sterile
787	Entire pancreas; weight, 35 Gm.	Gram-positive anaerobic bacilli	5.8	Survived; killed after 16 days; gram-positive anaerobic bacilli
396	Entire pancreas; weight, 32 Gm.	Gram-negative bipolar bacillus	8.0	Survived; killed after 40 days; peritoneal cavity sterile

of approximately the same weight and 10 an entire pancreas. Two of the 8 died and 6 survived. Of the 10 receiving the entire pancreas, 3 survived and 10 died.

It is apparent that under these conditions it requires the in vivo necrosis of from one-half to the whole of a pancreas regularly to cause the death of an otherwise healthy dog. It is true that the animal's own

pancreas has been undisturbed and that there is accordingly no factor of pancreatic insufficiency such as complicates the disease in man. It is, however, unlikely that this plays any part in such an acute process, since the complete removal of the pancreas in the dog is compatible with life for from five to ten days without special treatment. It is noteworthy that none of the animals died in less than eighteen hours. Apparently this much time at least is required for the production of a fatal toxemia, even in the presence of a sudden necrosis of the entire gland. Clinical reports of death within four or five hours of the onset of the disease suggest either that man is more susceptible to this type of toxemia or that other complicating factors are present. Cultures taken from the uncontaminated pancreas in 17 of these experiments revealed the presence of bacteria in all but 4, or an incidence of 76 per cent. Cultures taken from the peritoneal exudate in the immediate vicinity of the autolyzing gland in the animals that died were all positive, and it is doubtless significant that an anaerobic gram-positive bacillus resembling, if not identical with, B. welchii was obtained in each case.

In Vivo Autolysis of Fetal Pancreas.—The following experiment illustrates the innocuous effect of fetal pancreas:

A cesarean section was performed on a bitch near term and the entire pancreas from each of 4 of the fetuses secured. Careful aseptic precautions were observed, and cultures, both aerobic and anaerobic, proved the sterility of these fetal glands. The four glands were placed in the free peritoneal cavity of a dog weighing 9 Kg., and the abdomen was closed. The animal promptly recovered from the operation and displayed no subsequent ill effects. At autopsy six weeks later, no trace of the implanted tissue could be found.

Intraperitoneal Digestion of Sterile Autoclaved Pancreas.—Four experiments were performed in this group, the results of which are summarized in the following protocols:

Dog 985.—Aug. 15, 1930: This animal weighed 13.8 Kg. The abdomen was opened, and a portion of dog pancreas weighing approximately 18 Gm., which had been previously autoclaved at 15 pounds' pressure for twenty minutes, was placed in the peritoneal cavity, surrounded by omentum, and the abdomen closed. Cultures proved the implanted pancreas to be sterile. The animal promptly recovered and displayed no subsequent ill effects. The values for blood chlorides, sugar and nonprotein and urea nitrogen remained within normal range. The dog was electrocuted after twenty-one days, and autopsy revealed the implanted pancreas completely wrapped in omentum. It was somewhat reduced in amount and caseous in consistency.

Dog 991.—Aug. 15, 1930: This animal weighed 11.7 Kg. The abdomen was opened, and about 20 Gm. of fresh macerated dog pancreas was placed in the free peritoneal cavity. This pancreas had been first autoclaved at 15 pounds' pressure for fifteen minutes and found to be sterile by culture. The animal recovered promptly from the operation and continued in good health. The values for

blood chlorides, sugar and nonprotein and urea nitrogen remained within the normal range. The dog was electrocuted after twenty-one days, and autopsy revealed numerous caseous masses, the remains of the implanted pancreas, encapsulated in omentum.

Dog 414.—April 15, 1930: This animal weighed 6 Kg. The abdomen was opened, and about 35 Gm. of pancreas (the entire gland from a dog of somewhat larger size) was implanted in the free peritoneal cavity. This pancreas had been previously autoclaved at 15 pounds' pressure for fifteen minutes and found to be sterile by culture. The animal promptly recovered from the operation and continued in good health. The blood chemistry showed no deviation from the normal. The dog was killed after eleven days, and postmortem examination was performed immediately. The abdominal cavity was entirely normal and contained no free fluid. The implanted pancreas was still firm in consistency and about one half of its original size. It was partially encapsulated in omentum.

Dog 488.—April 15, 1930: This animal weighed 7 Kg. The abdomen was opened, and about 34 Gm. of pancreas (the entire gland from a dog considerably larger in size) was implanted in the free peritoneal cavity. This pancreas had been first autoclaved at 15 pounds' pressure for fifteen minutes and proved to be sterile by culture. The animal promptly recovered from the operation and did not display any subsequent ill effects. The blood chemistry remained within the normal range. The dog was killed after one hundred and fifty-one days, and immediate postmortem examination was performed. The peritoneal cavity was entirely normal, and no trace of the implanted pancreas could be found.

The rate of disintegration of the autoclaved pancreas placed in the abdominal cavity was obviously much slower than that of the fresh gland. This was to be expected since the heat was adequate to destroy all the pancreatic enzymes and effectually check autolysis. A complete digestion and removal of the necrotic sterile pancreas was, however, eventually brought about, presumably by ferments and cellular elements provided by the host, without the development of any symptoms of toxemia. This fact may be interpreted to indicate either that the end-products of the aseptic digestion of pancreas are not toxic, or, if they are toxic, that under these conditions they are elaborated so slowly that the defense mechanism of the body can detoxify and excrete them.

Toxicity of the End-Products of the Aseptic Digestion of Pancreas in Vitro.—Many observations have been made with respect to the end-products resulting from the autolysis, or self-digestion, of various tissues in vitro. For the most part, investigators have been interested in the chemical identification of some of the products of these digests, and determinations of their toxicity have, as a rule, not been made. The majority of such experiments, moreover, have been conducted without sufficient care to exclude bacterial contamination. Incubation between layers of toluene and chloroform has usually been adopted as a method for inhibiting bacterial growth, but adequate bacteriologic checks have rarely been made. It is clear from what has been found regarding the frequency of bacteria in the uncontaminated tissues of healthy ani-

mals that even the strictest aseptic precautions employed in removing organs cannot be relied on to exclude bacterial activity in autolysates free from antiseptics.

In the following experiments we have made an attempt to digest various sterile tissues in vitro with sterile gastric and pancreatic juice and to compare the toxicity of these digests with others containing the bacteria commonly found in the respective tissues in situ. Specimens of pancreas, liver and muscle were freshly secured and immediately autoclaved at 15 pounds' pressure for fifteen minutes. Gastric juice from an isolated stomach pouch (L. R. D. and J. C. E., 1930) and pancreatic juice from a fistula were freed from bacteria by Berkefeld filtration. The sterility of the resulting digests was checked by cultures for both aerobic and anaerobic organisms. It is probable that in acute pancreatic necrosis the responsible toxins are absorbed from the peritoneal cavity. Whether they pass directly into the capillaries draining into the portal system or into the lymphatics is unknown. It is fairly certain, however, that they must pass through a layer of endothelium before they reach the blood stream, and it is consequently probable that the injection of toxic fractions obtained from the pancreas into the peritoneal cavity more nearly reproduces the conditions of the disease studied than the injection of these fractions into a vein. In the latter case, it may be difficult to distinguish between the shock resulting from the intravenous injection of particulate matter and the toxemia of a soluble poison. For this reason the toxicity of each of these in vitro digests of pancreas, liver and muscle was determined by intraperitoneal injection. Mice were selected because the number of injections precluded the use of a larger animal. The results are summarized in table 4. To our mind, they prove conclusively that the digestion of pancreas, liver or muscle by gastric or pancreatic juice in the absence of bacterial contamination does not produce toxic end-products, whereas these develop in relatively large amount under the same conditions when the bacteria commonly found in these tissues are present.

Intraperitoneal Digestion of Autoclaved Pancreas by Sterile Pancreatic Juice.—The experiments described in the third section justify the conclusion that the end-products resulting from the digestion of the sterilized pancreas by the ferments of the peritoneal cavity are not sufficiently toxic to produce symptoms, or if toxic they are elaborated too slowly to produce toxemia. The heat of the autoclave has, of course, destroyed the pancreatic ferments, and one may reasonably raise the question: May not the digestion of sterile pancreas by the enzymes of the pancreatic juice produce different and more toxic chemical fractions than result from the slow disintegration of the autoclaved pancreas in the peritoneal cavity? It seems reasonable to infer that in clinical cases of acute pancreatic necrosis the dead cells are broken down in large

TABLE 4.—*Toxicity of the End-Products Resulting from the Aseptic Peptic and Tryptic Digestion of Pancreas, Liver and Muscle*

Mouse	Weight, Gm.	Material Injected Intraperitoneally*	Total Amount, Cc.	No. of Cc. per Gm. Body Weight	Result
1	29.5	Solution A (tryptic pancreas digest, aseptic)	1.0	0.034	No toxic effect
2	32.0	Solution A (tryptic pancreas digest, aseptic)	2.0	0.063	No toxic effect
3	30.6	Solution A (tryptic pancreas digest, aseptic)	3.0	0.098	No toxic effect
4	27.0	Solution A (tryptic pancreas digest, aseptic)	4.0	0.148	No toxic effect
5	29.0	Solution B (peptic pancreas digest, aseptic)	1.0	0.035	No toxic effect
6	32.4	Solution B (peptic pancreas digest, aseptic)	2.0	0.062	No toxic effect
7	30.5	Solution B (peptic pancreas digest, aseptic)	3.0	0.098	No toxic effect
8	19.0	Solution B (peptic pancreas digest, aseptic)	4.0	0.211	Dead in 1 hr.†
9	31.0	Solution C (pancreas autolysate, infected)	1.0	0.032	Dead in 20 hrs.
10	23.0	Solution C (pancreas autolysate, infected)	0.5	0.022	Dead in 19 hrs.
11	30.1	Solution C (pancreas autolysate, infected)	0.33	0.011	Dead in 19 hrs.
12	25.0	Solution C (pancreas autolysate, infected)	0.25	0.010	Dead in 19 hrs.
13	32.0	Solution D (tryptic pancreas digest, infected)	1.0	0.031	Dead in 20 hrs.
14	20.0	Solution D (tryptic pancreas digest, infected)	0.5	0.025	Dead in 18 hrs.
15	22.3	Solution D (tryptic pancreas digest, infected)	0.33	0.015	Survived
16	24.0	Solution D (tryptic pancreas digest, infected)	0.25	0.010	No toxic effect
17	23.0	Solution E (tryptic liver digest, aseptic)	1.0	0.043	No toxic effect
18	23.5	Solution E (tryptic liver digest, aseptic)	2.0	0.085	No toxic effect
19	26.8	Solution E (tryptic liver digest, aseptic)	3.0	0.112	No toxic effect
20	30.6	Solution E (tryptic liver digest, aseptic)	4.0	0.131	No toxic effect
21	32.0	Solution F (peptic liver digest, aseptic)	1.0	0.031	No toxic effect
22	26.4	Solution F (peptic liver digest, aseptic)	2.0	0.076	No toxic effect
23	20.2	Solution F (peptic liver digest, aseptic)	3.0	0.149	No toxic effect
24	24.0	Solution F (peptic liver digest, aseptic)	4.0	0.167	Dead in 19 hrs.
25	30.0	Solution G (liver autolysate, infected)	1.0	0.033	Dead in 20 hrs.
26	22.0	Solution G (liver autolysate, infected)	0.5	0.023	Dead in 18 hrs.
27	24.9	Solution G (liver autolysate, infected)	0.33	0.011	Dead in 3 hrs.
28	19.5	Solution G (liver autolysate, infected)	0.25	0.013	Dead in 2 hrs.
29	29.0	Solution H (tryptic liver digest, infected)	1.0	0.034	Dead in 20 hrs.
30	29.0	Solution H (tryptic liver digest, infected)	0.5	0.016	Dead in 7 hrs.
31	21.6	Solution H (tryptic liver digest, infected)	0.33	0.015	Survived
32	28.0	Solution H (tryptic liver digest, infected)	0.25	0.009	Dead in 46 hrs.
33	26.7	Solution I (tryptic muscle digest, aseptic)	1.0	0.037	No toxic effect
34	24.0	Solution I (tryptic muscle digest, aseptic)	2.0	0.083	No toxic effect
35	25.5	Solution I (tryptic muscle digest, aseptic)	3.0	0.176	No toxic effect
36	19.0	Solution I (tryptic muscle digest, aseptic)	4.0	0.211	No toxic effect
37	23.2	Solution J (peptic muscle digest, aseptic)	1.0	0.043	No toxic effect
38	25.0	Solution J (peptic muscle digest, aseptic)	2.0	0.080	No toxic effect
39	19.4	Solution J (peptic muscle digest, aseptic)	3.0	0.155	No toxic effect
40	28.4	Solution J (peptic muscle digest, aseptic)	4.0	0.141	No toxic effect
41	17.4	Solution K (muscle autolysate, infected)	1.0	0.057	Dead in 20 hrs.
42	33.0	Solution K (muscle autolysate, infected)	0.5	0.015	Survived
43	30.4	Solution K (muscle autolysate, infected)	0.33	0.011	Dead in 22 hrs.
44	22.0	Solution K (muscle autolysate, infected)	0.25	0.011	Dead in 3 hrs.
45	20.0	Solution L (tryptic muscle digest, infected)	1.0	0.050	Dead in 20 hrs.
46	23.0	Solution L (tryptic muscle digest, infected)	0.5	0.022	Dead in 18 hrs.
47	30.3	Solution L (tryptic muscle digest, infected)	0.33	0.011	Survived
48	15.0	Solution L (tryptic muscle digest, infected)	0.25	0.017	Dead in 19 hrs.

Solution A (tryptic pancreas digest, aseptic): Ten grams of fresh dog pancreas plus 20 cc. of Ringer's solution was autoclaved at 15 pounds' pressure for fifteen minutes. To this was added 50 cc. of fresh dog pancreatic juice, sterilized by passage through a Berkefeld filter. The mixture was incubated at 37 C. for sixty-eight hours, at which time the solid material was practically all in solution. Cultures of the digest all remained sterile. Eight cubic centimeters represented 1 Gm. of pancreas. The toxicity of the mixture was determined by intraperitoneal injections in mice.

Solution B (peptic pancreas digest, aseptic): Ten grams of fresh dog pancreas plus 20 cc. of Ringer's solution was autoclaved at 15 pounds' pressure for fifteen minutes. To this was added 50 cc. of pure dog gastric juice, sterilized by passage through a Berkefeld filter. The mixture was incubated at 37 C. for sixty-eight hours, at which time the pancreas was entirely digested and in solution. Cultures of the digest all remained sterile. Eight cubic centimeters represented 1 Gm. of pancreas.

Solution C (pancreas autolysate, infected): Ten grams of fresh uncontaminated dog pancreas plus 70 cc. of sterile Ringer's solution was incubated at 37 C. for sixty-eight hours. A scum formed on the surface of the solution, and this was found to contain many gram-positive cocci and gram-positive bacilli; 0.64 Gm. of solid material remained, so that 8.5 cc. represented 1 Gm. of pancreas. The toxicity of the filtrate was determined by intraperitoneal injections in mice.

Solution D (tryptic pancreas digest, infected): Ten grams of fresh uncontaminated dog pancreas plus 20 cc. of Ringer's solution plus 50 cc. of fresh dog pancreatic juice was incubated at 37 C. for forty-two hours. There was a luxuriant growth of bacteria in the mixture (gram-negative bacilli and gram-positive cocci); 1.26 Gm. of solid material remained undigested, so that 1 cc. represented 109 mg. of pancreas.

Solution E (tryptic liver digest, aseptic): Ten grams of fresh dog liver plus 20 cc. of Ringer's solution was autoclaved at 15 pounds' pressure for fifteen minutes. To this was added 50 cc. of fresh dog pancreatic juice, sterilized by passage through a Berkefeld filter. The mixture was incubated at 37 C. for sixty-eight hours, at which time the solid material was practically all in solution. Cultures of the digest all remained sterile. One cubic centimeter represented 125 mg. of fresh liver.

Solution F (peptic liver digest, aseptic): Ten grams of fresh dog liver plus 20 cc. of Ringer's solution was autoclaved at 15 pounds' pressure for fifteen minutes. To this was added 50 cc. of pure dog gastric juice, sterilized by passage through a Berkefeld filter. The mixture was incubated at 37 C. for sixty-eight hours, at which time the solid material was practically all in solution. Cultures of the digest all remained sterile. One cubic centimeter represented 125 mg. of fresh liver.

Solution G (liver autolysate, infected): Ten grams of fresh uncontaminated dog liver plus 70 cc. of sterile Ringer's solution was incubated at 37 C. for sixty-eight hours. A scum formed on the surface of the solution, and this was found to contain many bacteria (gram-negative bacilli); 0.81 Gm. of solid material remained, so that 1 cc. represented 115 mg. of fresh liver.

Solution H (tryptic liver digest, infected): Ten grams of fresh uncontaminated dog liver plus 20 cc. of Ringer's solution plus 50 cc. of fresh dog pancreatic juice was incubated at 37 C. for forty-two hours. There was a luxuriant growth of bacteria in the mixture (gram-positive bacilli and cocci); 1.65 Gm. of solid material remained undigested, so that 1 cc. represented 104 mg. of liver.

Solution I (tryptic muscle digest, aseptic): Ten grams of fresh dog muscle plus 20 cc. of Ringer's solution was autoclaved at 15 pounds' pressure for fifteen minutes. To this was added 43 cc. of fresh dog pancreatic juice sterilized by passage through a Berkefeld filter. The mixture was incubated at 37 C. for sixty-eight hours at which time the muscle was entirely digested. Cultures of the digest showed a meager growth of gram-negative bacilli. One cubic centimeter represented 137 mg. of muscle.

Solution J (peptic muscle digest, aseptic): Ten grams of fresh dog muscle plus 20 cc. of Ringer's solution was autoclaved at 15 pounds' pressure for fifteen minutes. To this was added 50 cc. of pure gastric juice, sterilized by passage through a Berkefeld filter. The mixture was incubated at 37 C. for sixty-eight hours, at which time the muscle was entirely digested. Cultures of the digest remained sterile. One cubic centimeter represented 125 mg. of muscle.

Solution K (muscle autolysate, infected): Ten grams of fresh dog muscle plus 70 cc. of Ringer's solution was incubated at 37 C. for sixty-eight hours. A scum formed on the surface of the solution, and this was found to contain a luxuriant growth of bacteria (gram-positive cocci and gram-negative bacilli); 0.6 Gm. of solid material remained, so that 1 cc. of the solution represented 118 mg. of muscle.

Solution L (tryptic muscle digest, infected): Ten grams of fresh dog muscle plus 20 cc. of Ringer's solution plus 50 cc. of fresh dog pancreatic juice was incubated at 37 C. for forty-two hours. There was a luxuriant growth of bacteria in the mixture (small gram-negative bacilli and large gram-positive cocci); 0.85 Gm. of solid material remained undigested, so 1 cc. of solution represented 114 mg. of muscle.

† Probably because of mechanical distention of abdomen.

part by the specific ferments of the gland. The following experiment was performed to test this possibility:

Dog 103.—May 13, 1931: This animal weighed 9.8 Kg. Blood was drawn for chemical examination, with the following result: chlorides, 290; sugar, 86, and nonprotein nitrogen, 32 mg. Under general ether anesthesia and with strict aseptic precautions, the abdomen was opened and a sterile pancreas digest introduced. This digest had been prepared as follows: Sixteen grams of fresh dog pancreas, sterilized in the autoclave at 15 pounds' pressure for fifteen minutes, plus 80 cc. of fresh, active pancreatic juice, sterilized by passage through a Berkefeld U filter, was incubated at 37 C. for sixty-nine hours. The pancreas was about two-thirds in solution, and cultures proved the mixture to be sterile. The entire mixture was placed in the free peritoneal cavity and the abdomen was closed. May 14: The animal recovered from the operation. Its general condition was good. The blood chlorides were 240; sugar, 109, and nonprotein nitrogen, 34 mg. May 26: The animal was in excellent condition. No evidence of toxemia appeared after operation. The animal was electrocuted, and immediate postmortem examination was performed. The peritoneal cavity was entirely normal, with no free fluid, no evidence of peritonitis and no trace of the pancreatic tissue digest.

Comment.—The experimental evidence obtained in this investigation, together with certain observations recorded in the literature, make it appear most probable that the toxemia of acute pancreatic necrosis is due to the absorption of toxic substances produced in the necrotic pancreas by the action of bacteria. Bacteria are present in the uncontaminated pancreas of a high percentage of normal rabbits and dogs, and it is likely that a similar situation obtains in man. In the 10 rabbits examined in this study, bacteria were found in the pancreas in every case, the colon bacillus being the predominant form. A somewhat lower incidence of bacterial contamination was found in the dog. Thirteen of the 17 examined, or 76 per cent, yielded positive cultures, while the cultures for 4 all remained sterile. It should be emphasized that search was made for both anaerobic and aerobic bacteria, and that no cultures were discarded short of two weeks' incubation. In a study made in this laboratory in 1926, Tower found bacteria in the fresh pancreatic tissue of dogs in 15 of the 16 animals operated on. It is probable that these bacteria are present in the duct system of the gland and that they have come from the duodenum, since they are similar in type to the ordinary intestinal organisms. It is clear that under normal conditions they evoke no signs of inflammation in the pancreas. In this respect they are similar to the organisms present in the liver, although it seems probable that in the latter case the bacteria are present in the reticulo-endothelial cells. It is significant that all cultures taken from the necrosing pancreatic tissue of the dogs that died from autolysis of the pancreas yielded an organism very similar to, if not identical with, B. welchii. The predominance of this organism may be due to its having overgrown other forms or to its escape from the gastro-intestinal tract in response to peritoneal irritation very much as occurs in biliary

peritonitis (Andrews, Rewbridge and Hrdina, 1931). The impression that the majority of cases of acute pancreatic necrosis in man are sterile seems to be due to prevailing theories regarding the cause of the disease rather than to the results of bacteriologic study. There have been surprisingly few attempts to culture the necrotic pancreas at operation or immediately after death at autopsy. Larkin (1898) found B. aerogenes-capsulatis, Germain and Christian (1904) streptococci, and Gunther (1909) and Brütt (1923) B. welchii either at postmortem examination or on culture of the peritoneal exudate at operation. The case reported by Gunther is especially interesting in this connection. Cholecystostomy was performed on a patient with acute pancreatitis. Many friable gallstones were found in the gallbladder, and a pure culture of B. welchii was obtained from the gallbladder bile. Death occurred two days after operation, and an autopsy was performed within an hour after death. The pancreas was necrotic, and there was extensive fat necrosis in the peritoneal cavity. A pure culture of B. welchii was again obtained from the necrotic pancreas and from the peritoneal exudate. D. B. Phemister (1930) operated on a patient who had a combination of acute pancreatitis and gangrenous cholecystitis in whom cultures taken from the peritoneal exudate revealed B. welchii in pure culture.

It is true that extracts of many fresh normal tissues yield substances that produce vasodepression and other toxic symptoms if injected into the blood stream of experimental animals. Goodpasture and Clark (1919) were able to secure such substances in extracts of the fresh dog pancreas. Bacteria could have played little or no part in the development of this toxicity, since there was scarcely sufficient time for bacterial activity and growth. It is significant, however, that it required an entire pancreas to yield one fatal dose for an animal of equal weight even when the extract was administered intravenously. As previously noted in cases of acute pancreatic necrosis, the poisons are absorbed from the peritoneal cavity and pass through at least one layer of endothelium before reaching the blood stream. The toxicity of tissue extracts is so greatly reduced by such passage that it is doubtful if the extract secured by Goodpasture and Clark would prove fatal if given in equal amounts intraperitoneally. It must also be kept in mind that the sudden injection of an extract obtained from the pancreas in which the entire dose of toxic material enters the blood stream within a few minutes hardly duplicates the situation which obtains in acute pancreatic necrosis and autolysis. In the latter case, it is reasonable to assume that the responsible poisons are continuously manufactured, liberated and absorbed during the entire period of from eighteen to thirty-six hours. The defensive mechanism of the body is much better able to cope with poisons of the type likely to develop in this instance when

they are slowly administered than when the maximum concentration is presented to the blood stream at once. The amount of toxic material in a watery extract of fresh dog pancreas has no effect if given intraperitoneally in graduated doses over a period of thirty-six hours to an animal of equal size. We must conclude that during the process of necrosis and autolysis of the pancreas there occurs a marked increase in the amount of soluble toxic material, or that some entirely new poisons are produced.

The experiments offer no support to the view that these toxic substances represent various fractions resulting from the digestion of the dead pancreas by the activated pancreatic juice. The product secured from the digestion of pancreas by pancreatic juice in the absence of bacteria was found to be practically nontoxic on intraperitoneal injection. The innocuous effect of implanting autoclaved pancreas or fetal pancreas, proved to be sterile by culture, into the peritoneal cavity is in harmony with this finding. The implantation of a mixture of ground autoclaved pancreas and active pancreatic juice, proved to be sterile by culture, into the peritoneal cavity without the production of toxemia represents almost a crucial experiment. It proves that neither active pancreatic juice nor the products arising from the digestion of dead pancreas by pancreatic juice within the abdomen are sufficiently toxic when the bacteria commonly found in the intact pancreas have first been removed. The conclusion seems inescapable that in some way these bacteria are necessary for the development of a toxemia in pancreatic necrosis. The exact nature of the poison or poisons remains a speculation. A large variety of toxic chemical fractions might be expected to develop in a mass of necrotic tissue being broken down both by pancreatic juice and by bacterial activity. The frequent finding of B. welchii in the necrotic pancreas suggests that its specific toxin may play a rôle in the disease. It seems more probable, however, that the major amount of responsible poisons will be found among the relatively large group of toxic organic bases that are known to be produced from the decomposition of proteins or protein split products by bacteria or their proteolytic enzymes.

OBSERVATIONS ON THE EFFECT OF ACUTE PANCREATIC NECROSIS ON CERTAIN CONSTITUENTS OF THE BLOOD

An attempt was made in 12 dogs to reproduce the symptoms of pancreatic poisoning by ligating the blood supply to varying amounts of the gland. The postoperative course was carefully observed, and daily determinations were made of the blood chlorides, sugar and nonprotein and urea nitrogen. The blood supply to the tail of the pancreas and to that portion which lies free in the duodenal mesentery was completely occluded in most cases, and careful transfixion sutures in the

duodenal pancreas further decreased its blood supply. Ten of the animals survived the operation and, aside from a moderate postoperative depression, completely recovered. Autopsy at varying periods of from two to five weeks later revealed no evidence of fat necrosis and surprisingly little change in the neighborhood of the pancreas. The free portions of the gland the blood supply of which had been completely interrupted were represented only by thin fibrous cords. The duodenal

TABLE 5.—*Effect of Ligation of the Blood Supply to the Dog's Pancreas on the Blood Chemistry* *

Dog	Days After Pancreas Ligation	Symptoms	Chlorides	Sugar	Nonprotein Nitrogen	Urea Nitrogen
220	0	Normal	301	..	33	15
	1	Lively	300	..	42	17
	2	Slight depression	223	..	82	47
	3	Slight depression	209	..	99	55
	4	Slight depression	204	..	83	53
	5	Lively	206	..	64	..
	7	Condition good	217	..	58	..
152	0	Normal	348	..	48	24
	1	Weak, depressed	289	..	48	23
	2	Weak, depressed	271	..	47	23
	3	Weak, depressed	284	..	43	21
	4	Condition good	278	..	48	23
	5	Condition good	...	..	41	20
999	0	Normal	303	160?	26	12
	3	Slight depression	302	88	23	..
	6	Condition good	316	90	31	14
993	0	Normal	275	79	26	12
	3	Slight depression	321	80	25	13
	7	Condition good	317	74	29	12
940	0	Normal	285	81	29	13
	2	Moderate depression	244	68	33	14
	5	Condition good	267	74	30	12
992	0	Normal	270	77	24	13
	2	Depressed	306	83	21	12
	6	Condition good	301	81	27	12
997	0	Normal	284	81	22	11
	2	Slight depression	251	105	29	..
165	0	Normal	370	..	30	10
	6 hrs.	Condition good	312	..	43	22
	23 hrs.	Severe depression	280	..	93	51
	25 hrs.	Moribund	297	..	118	57
	26 hrs.	Died				
211	0	Normal	303	..	40	14
	5 hrs.	Depressed	292	..	42	20
	24 hrs.	Marked depression	238	..	64	32
	28 hrs.	Marked depression	240	..	87	..
	31 hrs.	Moribund	238	..	86	..
	44 hrs.	Found dead				

* In the experiments necrosis of a part of the pancreas (from one third to one half) was produced by ligating the blood supply.

pancreas was otherwise grossly normal. The data are summarized in table 5.

Similar observations were made of the alterations in the blood chemistry produced by the intraperitoneal autolysis of implanted pancreas in the experiments previously described. The data are summarized in table 6. In both series a decrease in the concentration of blood chlorides and an increase in nonprotein and urea nitrogen were regularly found.

TABLE 6.—*Effect of In Vivo Autolysis of Pancreas on the Blood Chemistry*

Dog	Time After Pancreas Implantation	Symptoms	Chlorides	Sugar	Non-protein Nitrogen	Urea Nitrogen	Comment
986	0	Normal	230	84	33	14	Roughly ½ of a pancreas obtained from another dog was wrapped in omentum and abdomen closed
	24 hrs.	Vomiting, toxic	166	38	45		
	32 hrs.	Died					
948	0	Normal	255	..	24	10	Roughly ½ of a pancreas obtained from another dog was placed in the free peritoneal cavity and abdomen closed
	23 hrs.	Very toxic	200	..	54	33	
	47 hrs.	Very toxic	161	..	53	36	
	70 hrs.	Found dead					
949	0	Normal	278	..	27	13	About ½ of a pancreas obtained from another dog was placed in the free peritoneal cavity and abdomen closed
	23 hrs.	Very toxic	221	..	26	12	
	48 hrs.	Improved	254	..	30	14	
	72 hrs.	Purulent nasal discharge, cough	218	..	27	8	
	73 hrs.	Animal killed with ether; lobar pneumonia					
800	0	Normal	306	..	26	13	Roughly ½ of a pancreas obtained from another dog was placed in the free peritoneal cavity and the abdomen closed
	1 day	Slight depression	295	..	53	27	
	2 days	Slight depression	248	..	38	8	
	4 days	Condition good	240	..	23	13	
	6 days	Condition good	312	..	21	11	
	7 days	Condition good	326	..	19	11	
	9 days	Condition good	302	..	15	7	
	12 days	Condition good	329	..	19	12	
	19 days	Condition good	329	..	19	12	
	42 days	Condition good	313	..	17	10	
	42 days	Killed with ether					
916	0	Normal	287	..	25	11	About ½ of a pancreas obtained from another dog was placed in the free peritoneal cavity and the abdomen closed
	1 day	Slight depression	265	..	24	12	
	2 days	Slight depression	223	..	53	32	
	4 days	Condition good	222	..	45	26	
	6 days	Condition good	210	..	48	29	
	7 days	Condition good	268	..	36	16	
	9 days	Condition good	275	..	21	12	
	12 days	Condition good	316	..	20	10	
	19 days	Condition good	296	..	23	12	
	41 days	Killed with ether					
513	0	Normal	339	84	25	13	The entire pancreas obtained from a dog weighing 13.4 Kg. was placed in the free peritoneal cavity and the abdomen closed
	22 hrs.	Died					
732	0	Normal	296	90	29	12	The entire pancreas obtained from a dog weighing 21 Kg. was placed in the free peritoneal cavity and the abdomen closed
	18 hrs.	Died					
629	0	Normal	310	89	26	12	The entire pancreas obtained from a dog weighing 13.4 Kg. was placed in the free peritoneal cavity and the abdomen closed
	21 hrs.	Moribund	220	72	56	28	
	25 hrs.	Died					
419	0	Normal	200	..	24	11	The entire pancreas from another dog was placed in the free peritoneal cavity and the abdomen closed
	26 hrs.	Died					
588	0	Normal	295	..	22	13	An entire pancreas weighing 30 Gm. was placed in the free peritoneal cavity and the abdomen closed
	5 hrs.	Slight depression	271	..	24	7.5	
	22 hrs.	Moderate depression	234	..	52	24	
	29 hrs.	Moribund	317	..	75	50	
	34 hrs.	Died					
636	0	Normal	304	..	25	10	An entire pancreas weighing 35 Gm. was placed in the free peritoneal cavity and the abdomen closed
	6 hrs.	Moderate depression	303	..	24	18	
	22 hrs.	Found dead					
788	0	Normal	343	..	24	7	An entire pancreas weighing 30 Gm. was placed in the free peritoneal cavity and the abdomen closed
	6 hrs.	Slight depression	261	..	25	12	
	23 hrs.	Found dead					

TABLE 6.—*Effect of In Vivo Autolysis of Pancreas on the Blood Chemistry—Continued*

Dog	Time After Pancreas Implantation	Symptoms	Chlorides	Sugar	Nonprotein Nitrogen	Urea Nitrogen	Comment
548	0	Normal	273	..	26	12	An entire pancreas weighing 35 Gm. was placed in the free peritoneal cavity and the abdomen closed
	24 hrs.	Depression, marked weakness	275	..	45	25	
	29 hrs.	Condition better	224	..	48	24	
	2 days	Condition good	208	..	24	12	
	3 days	Condition good	278	..	23	11	
	4 days	Condition good	283	..	28	12	
	7 days	Condition good	274	..	27	12	
	19 days	Condition good	314	..	30	8	
787	0	Normal control	320	..	36	8	An entire pancreas weighting 35 Gm. was placed in the peritoneal cavity and the abdomen closed
	7 hrs.	Marked depression and weakness	266	..	27	11	
	24 hrs.	Very toxic	339	..	32	12	
	29 hrs.	Condition better	249	..	40	17	
	48 hrs.	Further improvement	256	..	24	0	
	54 hrs.	Condition good	256	..	19	8	
	72 hrs.	Condition good	276	..	18	6	
	79 hrs.	Condition good	266	..	16		
	96 hrs.	Condition good	253	..	17		
	103 hrs.	Condition good	263	..	15	9	
	5 days	Condition good	338	..	15		
396	0	Normal control	260	..	27	11	An entire pancreas weighing 35 Gm. was placed in the peritoneal cavity and the abdomen closed
	23 hrs.	Marked depression and weakness	251	..	28	..	
	29 hrs.	Condition better	226	..	29	12	
	48 hrs.	Further improvement	226	..	26	13	
	4 days	Moderate depression and weakness	168	..	39	20	
	9 days	Condition good	259	..	19	7	
	12 days	Condition good	272	..	20	8	
	19 days	Condition excellent	326	..	23	8	
	40 days	Condition excellent	302	..	24	12	

During the course of these studies an opportunity presented itself to examine the blood chemistry in a patient with a mild but undoubted case of acute pancreatitis. The pertinent features of the history are given here.

J. H., a man, aged 49, came to the hospital with symptoms and findings suggestive of chronic cholecystitis. Thirty-six hours later he experienced a sudden severe pain in the left upper quadrant of the abdomen, accompanied by a drenching perspiration and symptoms of vascular collapse. The blood pressure fell to 88 mm. systolic. A diagnosis of acute pancreatitis was made, and operation was performed immediately. The pancreas was indurated, and there were numerous areas of fat necrosis. No stones were found in the gallbladder or common bile duct. The wall of the gallbladder was thickened. A drain was placed in the gallbladder and in the lesser peritoneal cavity. Each twenty-four hours for the next five days 3,000 cc. of Ringer's solution was given subcutaneously or intravenously. The results of the chemical examination of the blood are summarized in table 7.

Here again, as in the animal experiments, a decrease in the concentration of blood chlorides and an increase in nonprotein and urea nitrogen are the most prominent changes. These alterations are similar to those which occur in acute intestinal obstruction or following the failure of reabsorption of gastric and pancreatic juice. It is probable that they can be accounted for in a similar way. The extensive perito-

neal irritation resulting from the in vivo autolysis of the pancreas might be expected to produce a profound reflex inhibition of gastro-intestinal motility. A paralytic ileus, more or less severe, is commonly found in acute pancreatitis in man. The relation of such disturbances in motility to the blood chemistry has been discussed by one of us in considerable detail elsewhere (L. R. D., 1930). Under normal conditions, the gastric and pancreatic secretions poured into the upper part of the alimentary tract are more or less completely absorbed in the intestine lower down. Water and inorganic salts, the principal constituents of these secretions, are not appreciably absorbed in the stomach, duodenum or even upper part of the jejunum. It is clear, then, that for reabsorption, the gastric and pancreatic juice must be carried by the motor activities of the intestine into the ileum and colon. Interference with this transport, such as occurs in paralytic ileus, must result in the loss of the various constituents of these secretions to the body either

TABLE 7.—*Blood Chemistry in a Case of Acute Pancreatitis*

Time After Operation, Days	Condition	Blood Chemistry				
		NaCl, Mg.	CO_2 Capacity, Cc.	Nonprotein Nitrogen, Mg.	Urea Nitrogen, Mg.	Sugar, Mg.
1	Sick, vomiting	335	55	58	36	...
2	Very sick, vomiting	458	50	102	76	125
3	Improved, no vomiting	464	57	86	66	...
4	Improved, no vomiting	402	68	76	52	152
5	Marked improvement	400	73	50	31	118

through vomiting or through accumulation of the lumen of the non-absorbing portions of the tract. The failure of reabsorption of the sodium and chloride ions present in gastric and pancreatic juice leads to the development of hypochloremia, alkalosis and dehydration, because the stomach (L. R. D. and I. C. E., 1930) and pancreas (Elman and McCaughan, 1927, and Gamble and McIver, 1928) have the property of separating these ions from the blood stream irrespective of their concentration there, even though such separation so greatly alters the chemical composition of the blood that life can no longer exist.

TREATMENT

While this investigation has been concerned primarily with the pathogenesis of acute pancreatitis, it may be worth while to note briefly certain inferences toward treatment that have suggested themselves. The poison or poisons responsible for this dread toxemia have not yet been defined in precise chemical terms, and until this is done there will be little hope of developing a specific antitoxic therapy. It is exceedingly important that this be done, since undoubtedly many patients have absorbed a fatal dose of this toxic material into the blood stream, and

it has become fixed in the tissue cells, before they come to treatment. The trial of B. welchii antitoxin would appear to be justified by the almost regular finding of this organism in the necrotic pancreas in these animal experiments. Needless to say, great caution should be observed in interpreting the results secured. It is our opinion, however, that not until we have secured an adequate therapy for the toxemias produced by the nonantigenic proteinogenous amines and other products of bacterial proteolysis will this part of the problem be solved.

At present, we are largely limited to attempts to prevent further injury to the pancreas and the entrance of additional poison into the blood stream. The suggestions of Archibald (1929) here seem most reasonable in the light of this study. Since in all probability the majority of cases are due to the passage of bile into the pancreatic ducts, it seems wise to reduce the pressure in the biliary tract and divert the bile and possibly the pancreatic juice as well to the exterior by means of cholecystostomy or choledochostomy. The drainage tube might well be connected to a negative pressure bottle. In view of the greatly increased susceptibility of etherized animals to histamine, it is probably safer to use local than general anesthesia. While the studies of Whipple and Goodpasture (1913) and Peterson, Jobling and Eggstein (1916) indicate that the abdominal exudate is nontoxic, we believe it is advisable to place drains about the pancreas. This is done not so much with the thought of draining away toxic material as to facilitate the formation of adhesions and the isolation of the necrotic pancreas from the remainder of the abdomen. The intravenous administration of physiologic solution of sodium chloride or Ringer's solution is advisable to correct the alterations in the blood chemistry and the dehydration accompanying the paralytic ileus. It is possible that the parenteral administration of large amounts of salt solution with the ensuing diuresis may facilitate the excretion of soluble toxic chemicals from the blood stream and so exert a dual beneficial effect. Repeated gastric aspirations prevent overdistention and enable the stomach to recover its tonus more quickly.

CONCLUSIONS

It is probable that about 60 per cent of the cases of acute pancreatic necrosis in man arise in patients with antecedent chronic biliary tract disease. Of these, it is likely that 10 per cent develop a common channel as a result of the impaction of a gallstone in the ampulla and a majority of the remainder a similar continuous channel through spasm of the sphincter of Oddi or edema of the papilla. In this group, the immediate cause of the necrosis is the passage of bile over into the pancreatic ducts which is made possible not so much by a difference in secretory pressures of the liver and pancreas as by the fact that the

intraglandular anastomoses between the ducts of Wirsung and Santorini make the secretory pressure of the pancreas ineffectual in the majority of cases. Bile produces necrosis of the pancreatic parenchyma because of the local cytolytic and destructive properties of the bile salts and not through activation of the intraductal trypsinogen of the pancreatic juice. The toxic effect of the bile salts is neutralized by the proteins of the blood serum, so that hemorrhage and exudation are protective phenomena. The digestion of the protective proteins of the serum by the proteolytic enzymes of the pancreatic juice frees the bile salts for further destructive action, and this probably accounts for the greater susceptibility of the pancreas to biliary necrosis than is found for other glandular organs. A typical pancreatic necrosis may, however, be produced by a variety of factors, listed in the foregoing discussion, in which bile plays no part. The discovery of instances in which a common continuous channel of the bile and pancreatic ducts is an anatomic impossibility can, accordingly, not be construed as evidence against the bile factor in pancreatitis, since it merely shows that it is not operative in the particular cases studied. There is no good evidence that the intraductal or intraglandular activation of trypsinogen will cause self-digestion of the pancreas. Active trypsin was found to be incapable of digesting living tissues. It is probable that trypsin has no corrosive properties in itself which would injure living cells and that it acts only as a catalyst in facilitating the hydrolysis of proteins by the alkali of the pancreatic juice. The locally destructive action of pancreatic juice is dependent on its concentration of alkali just as the corrosive effect of gastric juice is dependent on its concentration of free acid.

It is probable that irrespective of whether the necrosis of the pancreas is due to the invasion of bile, to trauma, to vascular injury or to infection, the cause of the resulting toxemia is the same. The amount of pancreatic juice or of its constituent enzymes which could be present in the necrotic pancreas is insufficient to account for the toxic effect. Inactive pancreatic juice was found to be nontoxic if allowed to flow into the free peritoneal cavity. The active lipase of this secretion was unable to digest the lipoid envelop of living cells and produce necrosis. The areas of so-called fat necrosis found probably represent already dead cells the fat of which has been converted into glycerin and fatty acids by the pancreatic steapsin, after which the fatty acids have combined with calcium to form soaps. It is probable that in acute pancreatitis the fat necrosis is due more to the destructive action of bile than to that of pancreatic juice. The digestion of the fat is brought about by the latter secretion. The intraperitoneal injection of actively proteolytic pancreatic juice was found to be no more toxic than the intraductal secretion if bacterial contamination was avoided. As much

as 110 cc. of a Berkefeld filtrate of active pancreatic juice was injected into the free peritoneal cavity without causing toxemia. The end-products of the partial or complete digestion of the pancreas by active pancreatic juice are not sufficiently toxic, if placed in the peritoneal cavity, to cause death. The in vivo autolysis of sterile fetal pancreas and the intraperitoneal digestion of autoclaved pancreas by sterile pancreatic juice did not produce toxemia. The uncontaminated pancreases of 10 living, adult, normal, rabbits yielded positive bacterial cultures in every instance, or 100 per cent. In 13 of 17 dogs similarly examined, bacteria of various types were found in the uncontaminated pancreas. These bacteria were similar to those common to the intestinal tract. B. welchii was especially prevalent. The toxemia resulting from experimental in vivo autolysis of the pancreas is chiefly due to the presence of these organisms, which proliferate in the necrotic tissue. It is possible that the toxin of B. welchii may contribute to the toxic effect, but it seems probable that the major part of the toxemia is due to the group of proteinogenous amines and similar substances arising from the bacterial decomposition of proteins or their split products.

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EXPERIMENTAL OBSTRUCTION OF JEJUNUM

EFFECT OF ADMINISTRATION OF WATER ON LENGTH OF LIFE AND CHANGES IN CHEMICAL COMPOSITION OF BLOOD

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It is well recognized that there is a decrease in chlorides and an increase in the carbon dioxide-combining power and in the nonprotein nitrogen and the urea nitrogen of the blood in intestinal obstruction. The rôle played by water, when administered by mouth, on the extent of these changes and on length of life has been little studied. A more thorough investigation was thought indicated, particularly since determinations of the chemical composition of the blood are being increasingly used as a guide for treatment of obstruction of the pylorus and small bowel.

In an earlier study of the changes occurring in the blood incident to high intestinal obstruction, the average length of life of dogs was observed.[1] These animals were allowed as much water as they wanted, and the average length of life of thirty-five dogs in which the upper part of the jejunum was obstructed was 6.8 days. Hartwell and Houguet[2] obstructed the jejunum of dogs from 10 to 30 cm. below the pylorus and found that few lived longer than five days. They also found that dogs deprived of food from forty-eight to seventy-two hours before obstruction would die as early as those fed from ten to twenty hours before obstruction. Wangensteen[3] says that the average length of life of dogs with high intestinal obstruction is from three to four days. Dragstedt and Moorhead[4] obstructed the duodenum of dogs below the pancreatic duct, and all the animals died in less than ninety-six hours.

From the Department of Surgery, University of Kansas School of Medicine.

1. Haden, R. L., and Orr, T. G.: Chemical Changes in the Blood of the Dog After Intestinal Obstruction, J. Exper. Med. **37**:365, 1923.

2. Hartwell, J. A., and Houguet, J. P.: An Experimental Study of Intestinal Obstruction, Am. J. M. Sc. **143**:357, 1912.

3. Wangensteen, O. H.: The Diagnosis and Treatment of Acute Intestinal Obstruction, Northwest Med. **30**:389, 1931.

4. Dragstedt, L. R., and Moorhead, J. J.: Immunity in Intestinal Obstruction, J. Exper. Med. **27**:359, 1931.

MATERIALS AND METHODS

In this study intestinal obstruction was produced in twelve healthy dogs by sectioning and inverting the cut ends of the jejunum 15 cm. below the ligament of Treitz. All operations were done under ether anesthesia with aseptic technic. Six dogs were allowed water ad libitum after the operation, and six were entirely deprived of water. None of the dogs received food after the operation, nor was any food given twenty-four hours prior to the operation. The animals were kept in clean metabolism cages, and the body weight taken daily. An autopsy was always performed. Peritonitis was never a complicating factor.

TABLE 1.—*Obstruction of the Upper Jejunum of the Dog When No Water Was Allowed*

Dog	Day After Obstruction	Blood, Mg. per 100 Cc.			Carbon Dioxide-Combining Power, per Cent by Volume	Body Weight, Kg.	Comment
		Chlorides, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.			
1	0	510	12.3	73.2	43.9	13.85	Fat dog; length of life, 36 hours
	1	442	19.6	75.4	49.5	12.75	
2	0	515	17.1	71.4	45.8	7.36	Moderately fat dog; length of life, 56 hours
	1	490	14.4	93.0	55.1	6.75	
	2	510	55.6	119.0	46.5	6.30	
3	0	515	11.4	75.7	51.4	11.30	Fat dog; length of life, 60 hours
	1	460	8.1	83.3	52.3	10.55	
	2	460	18.5	100.0	51.2	10.40	
4	0	510	7.7	67.7	46.2	8.80	Moderately fat dog; length of life, 80 hours
	1	467	7.4	109.8	50.9	8.45	
	2	400	13.3	81.6	50.7	8.02	
	3	450	15.7	119.0	57.5	7.75	
5	0	542	11.9	56.5	47.7	7.25	Fat dog; length of life, 120 hours
	1	467	9.0	76.9	52.5	6.85	
	2	480	13.9	52.2	52.8	6.65	
	3	505	15.7	62.5	57.5	6.41	
	4	480	16.3	64.9	54.7	6.13	
	5	470	46.7	88.2	52.0	..97	
6	0	520	9.9	60.7	49.0	13.25	Fat dog; length of life, 130 hours
	1	463	7.5	111.0	52.8	12.80	
	2	380	12.5	60.6	54.7	12.20	
	3	420	14.5	100.0	55.6	11.63	
	4	425	59.1	94.3	55.1	11.24	
	5	385	84.0	80.4	50.2	11.05	

Blood for chemical analysis was obtained from the jugular vein before operation and at twenty-four hour intervals thereafter until the death of the animal (tables 1 and 2). The blood chlorides were determined on the tungstic acid filtrate, as suggested by Gettler.[5] The blood for the carbon dioxide-combining power was collected under oil and determined by the method of Van Slyke and Cullen;[6] the urea nitrogen was determined by the Van Slyke and Cullen[7] modi-

5. Gettler, A. O.: Method for Determination of Death by Drowning, J. A. M. A. **77**:1650 (Nov. 19) 1921.

6. Van Slyke, D. D., and Cullen, G. E.: Studies of Acidosis: The Bicarbonate Concentration of the Blood Plasma; Its Significance and Its Determination as a Measure of Acidosis, J. Biol. Chem. **30**:289, 1917.

7. Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of Urease and Its Use for Rapid and Accurate Determination of Urea, J. A. M. A. **62**:1558 (May 16) 1914.

fication of the Marshall method, and the sugar by the method of Folin and Wu.[8] The protein-free blood filtrates were made by Haden's modification of the original Folin-Wu technic.[9]

TABLE 2.—*Obstruction of the Upper Jejunum of the Dog When the Animals Were Permitted to Drink Water ad Libitum*

Dog	Day After Obstruction	Blood, Mg. per 100 Cc.			Carbon Dioxide-Combining Power, per Cent by Volume	Body Weight, Kg.	Comment
		Chlorides, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.			
1	0	480	12.6	59.4	48.5	7.45	Moderately fat dog; length of life, 66 hours
	1	444	32.8	81.3	40.2	7.05	
	2	383	36.4	72.2	53.7	6.75	
2	0	525	18.2	68.1	42.5	7.65	Moderately fat dog; length of life, 116 hours
	1	407	18.5	80.9	47.7	7.20	
	2	385	27.6	87.3	63.2	6.90	
	3	365	50.8	78.7	67.2	6.85	
	4	298	85.3	117.6	67.1	6.60	
	5	269	122.0	207.0	41.6	6.15	
3	0	530	7.7	85.1	53.7	9.00	Moderately fat dog; length of life, 158 hours
	1	475	6.9	84.4	52.3	8.76	
	2	455	4.7	77.1	53.1	8.83	
	3	460	7.2	62.1	52.4	8.55	
	4	392	13.5	84.0	51.8	8.25	
	5	351	32.1	105.1	58.1	7.95	
	6	293	55.2	114.1	65.5	7.60	
4	0	485	12.2	59.7	43.7	9.95	Moderately fat dog; length of life, 200 hours
	1	470	13.7	77.8	48.4	9.85	
	2	395	12.2	72.7	48.1	9.65	
	3	422	9.1	94.4	46.3	9.75	
	4	456	5.5	80.3	58.4	9.40	
	5	435	9.8	79.9	52.8	9.38	
	6	456	9.8	70.4	50.6	9.05	
	7	430	10.1	66.8	54.0	8.95	
	8	400	10.3	62.7	54.2	8.65	
	9	425	33.1	128.1	65.4	8.53	
	10	429	41.1	351.0	35.2	7.93	
5	0	460	7.8	62.5	51.3	12.55	Fat dog; length of life, 264 hours
	1	418	9.3	77.6	57.5	12.50	
	2	379	8.4	67.2	59.3	12.25	
	3	400	10.6	67.8	62.1	12.15	
	4	429	13.3	76.1	66.6	11.80	
	5	380	13.8	76.6	70.6	11.35	
	6	349	11.7	75.7	70.3	11.15	
	7	350	18.7	71.3	71.4	10.85	
	8	330	14.1	79.4	72.8	10.65	
	9	248	44.4	100.2	78.1	10.20	
	10	271	56.8	104.8	79.1	9.93	
	11	202	72.8	164.0	101.2	9.35	
6	0	490	6.1	70.1	57.2	16.80	Fat dog; length of life, 182 hours
	1	408	8.9	74.2	59.0	16.40	
	2	425	15.3	67.9	56.7	15.95	
	3	440	15.9	57.6	60.6	15.75	
	4	412	32.7	65.8	58.7	15.65	
	5	391	58.1	65.2	58.1	15.35	
	6	344	59.0	86.6	54.4	15.35	
	7	280	62.8	98.0	59.3	14.00	
	8	295	93.8	113.8	64.5	13.88	

8. Folin, O., and Wu, H.: A System of Blood Analysis, J. Biol Chem. **38**:81, 1919.

9. Haden, R. L.: A Modification of the Folin-Wu Method for Making Protein-Free Blood Filtrates, J. Biol. Chem. **56**:469, 1923.

OBSERVATIONS AND COMMENT

As the experiment progressed, the blood chlorides of the dogs receiving no water showed only a small drop compared with those of the dogs that were allowed water. The greater fall in chlorides found in the animals receiving water is probably due to a washing of the chlorides from the stomach and upper intestine by persistent vomiting. Dogs receiving water showed a greater rise in carbon dioxide-combining power. The urea nitrogen showed the characteristic increase in both series. The increase was generally most marked in the animals living the longest. There was an increase in blood sugar in every animal in each series. The greatest change was found in the animals living longest.

In spite of the lesser effect on the chemical composition of the blood shown in the animals to which no water was given, these animals did not live so long as those that were allowed water and that showed marked changes in the blood. The average length of life of the animals not receiving water was eighty-two hours, while those receiving water lived an average of one hundred and seventy-two hours.

A study of the body weights shows that the rate of loss in weight was not so rapid in the animals receiving water as in those that did not. This would point to some absorption of water from the upper gastro-intestinal tract, which may in part explain the greater length of life of these animals. The state of nutrition of the animals did not appear to have any bearing on the length of life.

SUMMARY

1. The upper part of the jejunum was obstructed in twelve healthy adult dogs. Six of them were deprived of both food and water, and six were deprived of food but given water freely.

2. The animals deprived of water showed relatively little change in the blood chlorides, carbon dioxide-combining power and sugar compared to the animals to which water was freely administered.

3. The animals showing great change in the chemical composition of the blood lived longer than the animals showing little change.

4. The rate of loss in body weight was slower in the animals receiving water than in the animals deprived of water. This would suggest that water absorbed from the upper gastro-intestinal tract helped to prolong the lives of the animals.

5. These experimental findings suggest that continuous lavage of the stomach in acute intestinal obstruction is a beneficial part of the treatment.

THE PART PLAYED BY URETERAL INFLAMMATION IN DILATATION OF THE URETER

A POSTMORTEM STUDY

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That dilatation of the ureter will result from obstruction is apparent, but that it may be acquired in the absence of any form of mechanical obstruction is perhaps less obvious and at first glance paradoxical. Atony of the ureter, by which is meant loss of functional ability of the muscle of the ureter, whereby peristalsis is weak or absent, was first recognized by Russian observers as a cause of ureteral dilatation. Further, they conceived the idea that atony and dilatation may result from inflammation. In this country Braasch repeatedly has called attention to this inflammatory dilatation, but by most observers such a possibility has not been appreciated or has been frankly doubted.

It is also true that certain obstructive factors commonly assumed to cause ureteral dilatation are in fact of obscure mechanism. Thus, there has been much speculation over the ureteral dilatation which accompanies pregnancy, and also over that which occurs with prostatic obstruction. The frequent association of these questionable obstructive factors with ureteral infection makes any appraisal of the part the latter may play a matter of interest. It was for the purpose of investigating these aspects of ureteral dilatation that I undertook this study. The extensive review of the literature which preceded my own work is omitted from this paper.

MATERIAL

The material investigated was obtained at necropsy in one hundred unselected cases. The causes of death were representative of many types of disease. Sixty-eight subjects were males and thirty-two were females. All decades of life up to the ninth were represented; there were eight subjects in the first decade.

METHOD

In each case the ureters were carefully inspected in situ. Their relation to surrounding structures and the relation of the state in which they appeared to any disease of surrounding structures were noted. This included attention to the

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presence of supernumerary vessels to the kidney, to the effect of pressure from the ductus deferens, and to the seminal vesicles, bladder, prostate gland, urethra and female pelvic structures. A no. 24 French urethral sound was passed in each case in which, judging from the history or from the lesions found, urethral stricture might have been a factor.

The ureters were then carefully removed, with the kidneys, bladder and prostate gland attached, and the bladder was opened anteriorly for inspection. In eighty-eight cases, ureterograms or pyelo-ureterograms were then made in the following manner:

The pelves and ureters were first gently stripped to insure complete emptying. Tips of Garceau catheters were tied lightly within the ureteral orifices by a stitch taken in the surrounding vesical tissue, and the ureters and pelves were filled by gravity from a height of 34 cm. A 30 per cent solution of sodium bromide was used. This solution at this height has a pressure equivalent to 30 mm. of mercury. This pressure filled the ureter gently. In two cases incomplete filling was noted. However, the least possible pressure seemed desirable, and this pressure probably approximated that used clinically.

The contour of the ureter was observed as it filled, and the amount of solution required to fill the pelvis and ureter was recorded. The place where the internal diameter of the ureter was smallest was found, and was measured by passing ureteral bulbs. The bulbs were tried in decreasing sizes on the French scale, until one was found which would enter and pass up the ureter without meeting obstruction to very gentle pressure. The largest bulb which would just pass in this way was taken as the smallest diameter of the ureter.

The widest diameter of each ureter was measured after the ureter had been opened longitudinally along its anterior aspect. By gently extending the ureter to the limits of its lateral elasticity, the internal circumference could be measured and the diameter calculated. In a third of the cases the diameter at the narrowest point was measured in this way. The diameter of the ureter when measured on the roentgenogram was found to correspond closely with the internal diameter measured on the ureter at the same level. Discrepancies which occurred in some cases were due to the filled ureter being markedly oval rather than cylindric.

From two to six cross-sections, including the whole circumference, were taken from various levels of each ureter for microscopic study. These were stained with hematoxylin and eosin, and by van Gieson's method for fibrous tissue.

The measurements and roentgenograms were completed in from two to four hours after death in most cases, so that postmortem changes affecting the distensibility of the ureter were negligible, except as will be referred to later. The average examination was complete within six hours after death, and not more than twelve hours elapsed between death and completion of the examination in any case. With each case the history was reviewed for symptoms or clinical findings possibly referable to the urinary tract, and especially for lesions of the central nervous system which might affect the nervous mechanism of the urinary tract.

The data from which information was drawn may be summarized as follows: (1) clinical history and examination, (2) inspection of the ureter in situ, (3) contour of the filled ureter after removal, (4) the measured internal diameter, (5) measurements of the capacity of the ureter and pelvis, (6) ureteropyelograms (post mortem) and (7) microscopic sections.

In deciding the status of any ureter, it must be remembered that individual variations in form and size are great, and that any set standards for the normal, although helpful, must be arbitrary and may mislead. Since it was realized that normally narrow ureters may become dilated and still be in the range of many

of the quoted normal figures, and that ureters in the same person, although usually resembling each other in general contour and type, need not do so, each ureter was considered on its own merits, in the light of data accumulated from all available sources.

DIAMETER

Measurements of internal diameter were made of seventy-two normal right ureters and of seventy-three normal left ureters of adult subjects. Measured at the widest point of each ureter, the average diameter of the right ureter was 6.2 mm., and that of the left ureter, 5.6 mm. The variation was from 3 to 9.5 mm. Measured at the narrowest point of each ureter, the average diameter was 2.6 mm. for both right and left ureters, the variation being from 1.3 to 4.6 mm. The situation of the narrowest point of the ureter was at the orifice in 31 per cent of cases and in the lowest 4 cm. in 82 per cent of cases.

CAPACITY

Measurements of the capacity of the ureter and pelvis of adults were made in forty-nine cases on the right side and in fifty-three cases on the left side. The average capacity on the right side was 11.5 cc., and that on the left, 10.5 cc. The variation on the right side was from 5 to 20 cc., and that on the left side was from 4.5 to 18 cc., except in one case. In this case, in which the ureters and pelves must be considered to have been normal, the capacity was 30 cc. The subject was very large, and died of myocardial failure. The right kidney weighed 187 Gm., and the left, 227 Gm. The kidneys appeared normal, except that a large, solitary cyst was observed on the convex border of the left kidney. There was no reason to believe that this had in any way interfered with renal drainage. There was considerable hypertrophy of the prostate gland, but without evidence of obstruction to the bladder. The ureters were normal. The large capacity was evidently due to the unusual number of large, branching calices. The capacity of the corresponding kidney could not be accurately measured because of the readiness with which pyelovenous backflow occurred.

OCCURRENCE OF URETERAL STRICTURE

Clinical determination of ureteral stricture has been by the "hang" of the ureteral bulb and by the ureterographic shadow. The fallacy of the bulb method was demonstrated by Frater in postmortem study of ninety-three cases, and his experience was confirmed in the present series. Repeatedly, in cases in which hang was obtained, there was no microscopic or gross evidence of stricture.

The pyelographic evidence of ureteral stricture is localized narrowing of the ureteral shadow, with dilatation of the ureter above. Ureteral

spasm is distinguished from stricture by absence of dilatation above the narrowing. Incomplete filling must also be distinguished.

In considering the question of ureteral stricture, it has been assumed heretofore, in postmortem studies, that the factor of spasm is eliminated. That spasms do occur post mortem was repeatedly demonstrated in this series of ureters.

Narrowings of the ureterographic shadow occurred not infrequently in this series. They suggested spasm in that there never was dilatation above them. Also, they occurred more often in ureterograms taken soon after death than in those taken after some delay. In one case the narrowing was sufficient completely to block injection of the medium until a pressure of 100 mm. of mercury was reached, when a normal renal pelvis was outlined above.

In another case it was possible gently to expose the right ureter half an hour after death. Pinching with forceps sent the upper third of the ureter into visible spasm, which persisted until the pyelogram was taken an hour later. On opening the ureter at the point of narrowing, the mucosa was seen to be in the longitudinal folds characteristic of contraction. Microscopic sections taken at these narrow points showed no evidence of stricture; that is, the ureteral structure was normal, without increase in fibrous tissue or evidence of inflammatory process. Evidently, then, these narrowings are caused by spasm.

Stricture of the ureter of intrinsic inflammatory origin has been the subject of many clinical reports and much controversy in the past. As has just been shown, the clinical difficulties of demonstration of stricture also exist for the gross determination of stricture after death. In the latter case, however, microscopic check on the diagnosis is possible. With inflammatory stricture there should be microscopic evidence of its presence. Such stricture, due to localized increase of connective tissue, the result of a primary inflammatory process in the ureteral wall, was not found in this series of cases.

Narrowings of the ureteral lumen which were evidently interfering with ureteral function, since there was dilatation above them, occurred in four cases. Two of these were strictures at the orifice, the result of vesical disease. In one of these two cases, the narrowing was the result of infiltration by a tumor, and in the other, of inflammatory reaction to surgical diathermy. In the other two cases the narrowing was caused by involvement of the ureter in periureteral scar tissue which had formed postoperatively.

URETERAL DILATATION

In twenty-five of the hundred cases, dilatation of one or both of the ureters or pelves was found. In a number of cases, at necropsy, the cause of the dilatation was found to be obstruction. In other cases,

obstruction had been present previously, as was noted from the histories of the cases. In another group of cases, however, there was neither obstruction nor a history of obstruction. Consideration of a number of cases of this group made it seem evident that infection of the ureteral wall, leading to atony, was the cause of the dilatation. In other cases, in which obstruction was present, inflammation undoubtedly was a contributory factor.

The causes of ureteral dilatation in this series may be grouped as follows: stricture of the ureter resulting from local causes, four cases; mechanical obstruction from an aberrant renal vessel, from a fibromyoma of the uterine cervix or from a vesical tumor, one case each; stone with ureteritis, two cases; pelvic inflammation involving a length of the ureter, two; pregnancy, one case; multiparity associated with ureteritis, four cases; prostatic hypertrophy associated with infection, three; insufficiency of ureteral valve, due to inflammation, two; inflammation of the ureter with no other associated cause, four; neurogenic origin (questionable), one case, and congenital origin, one.

The following cases are selected as illustrative of the part played by inflammation in causing dilatation of the ureter.

REPORT OF CASES

CASE 1.—*Prostatism and ureteral infection.*

A man, aged 74, with a history of obstructive vesical symptoms for eight years, died of renal insufficiency ten days after cystostomy.

At necropsy, little, if any, enlargement of the prostate gland was found. It was, however, inflamed and contained many calculi. There were marked hypertrophy of the vesical wall, with many cellules, and severe cystitis. Both ureters and renal pelves were found enormously dilated. On the right side the capacity was 75 cc., and on the left side, 95 cc. The right ureter varied in diameter from 3.3 mm. at the orifice to 16.6 mm. at its widest part. The diameter of the left ureter varied from 3.6 mm. at the orifice to 13 mm. at its widest part. The mucosa of each appeared injected and edematous throughout.

Microscopically, both ureters presented the appearance of acute infection superimposed on chronic infection. The submucosal layer was edematous and infiltrated with polymorphonuclear leukocytes. There was much young connective tissue with large and small lymphocytes. The muscular layer was poorly stained and infiltrated with polymorphonuclear leukocytes. The adventitia was characterized by groups of lymphocytes and young connective tissue cells. The prostate gland was evidently obstructing the bladder. However, it was notable that although the wall of the bladder was greatly thickened the diameter of the intramural portion of the ureter was more than the average. Such a condition is difficult to reconcile with the view that the hypertrophied vesical wall obstructs the ureters. The idea that the lower part of the ureter becomes distorted by enlargement of the prostate gland is not applicable here, since actual enlargement of this gland was negligible. Whatever the cause of obstruction to the ureters in cases of prostatic disease, infection may be considered a frequent contributory factor to the dilatation.

CASE 2.—*Incompetence of the ureteral orifice caused by inflammation.*

A man, aged 67, died of acute diffuse pyelonephritis and bronchopneumonia. Nine years previously a papilloma had been removed from the bladder. Since then he had had increasing frequency and occasional hematuria on straining.

Necropsy disclosed suppuration but only slight enlargement of the prostate gland. The bladder was of small capacity, of irregular shape, much scarred and acutely inflamed. The right ureteral orifice was gaping and rigid. Regurgitation through it had been demonstrated a week before death. A pyelogram made post mortem gave evidence of a normal left ureter and pelvis. The right ureter and pelvis were markedly dilated, with a capacity of 35 cc. (fig. 1). The internal diameter of the right ureter varied from 3.3 to 11 mm. The kidney was atrophied, and weighed only 50 Gm. Sections of the intramural portion of the right ureter,

Fig. 1 (case 2).—Right ureteral dilatation due to gaping ureteral orifice, the result of infection.

as well as of the same ureter higher up, contained masses of lymphocytes and young connective tissue cells in all the layers. It was evident that the incompetence of the ureteral valve was due to its inflammation.

CASE 3.—*Dilatation due to inflammation (right); dilatation due to obstruction (left).*

A man, aged 59, died of coronary sclerosis. It was known that he had had a carcinoma of the bladder for five years, but the situation of the growth and the patient's condition made operation inadvisable.

Necropsy disclosed a solid, sessile tumor 4 cm. in diameter situated on the base and left posterior wall of the bladder. The left ureteral orifice was obscured at the edge of the growth. There were three smaller implants in the dome of the bladder. Intense cystitis was present. The left ureter and pelvis were enormously dilated, with a capacity of 650 cc. Only a shell of the renal tissue remained. The dilatation of the ureter was notably even throughout.

Fig. 2 (case 3).—Enormous dilatation of the left ureter caused by obstruction. Irregular dilatation of the right ureter caused by inflammation without obstruction. The right ureter is on the left of the picture.

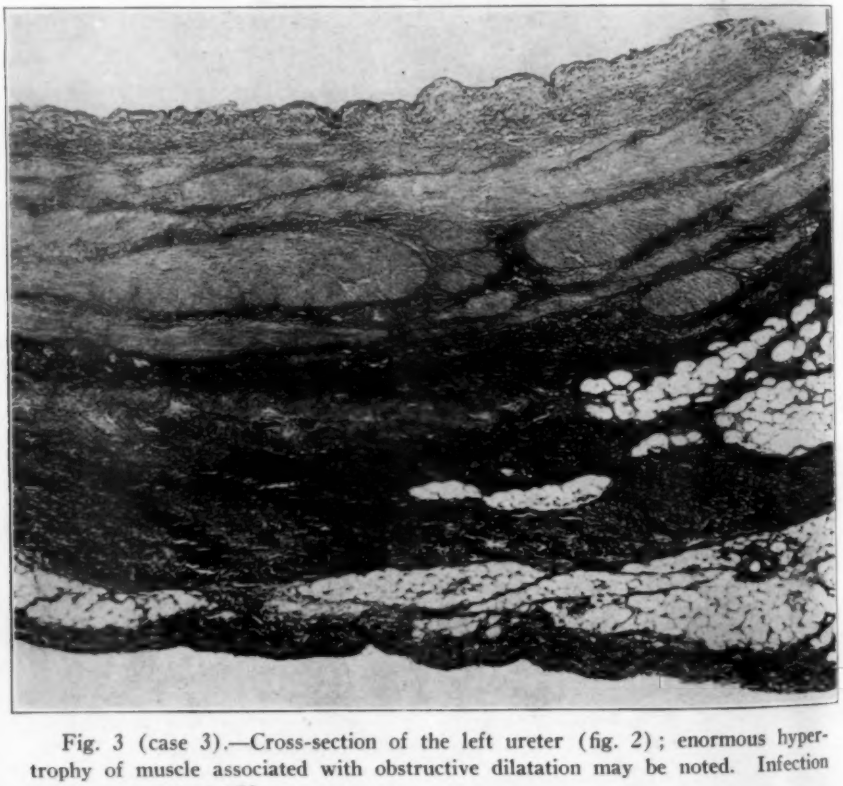

Fig. 3 (case 3).—Cross-section of the left ureter (fig. 2); enormous hypertrophy of muscle associated with obstructive dilatation may be noted. Infection was not present; × 38.

The right ureter, however, was not obstructed, and dilatation of its lower half was evident. The dilatation here was not so large as that of the left ureter, and was irregular. The internal diameter of the right ureter varied from 3 to 9.6 mm. At the orifice, the diameter was 4.6 mm. The capacity of the ureter and pelvis was 18 cc. Grossly, there was some injection of the ureteral mucosa (fig. 2).

Microscopic sections from various levels of the obstructed left ureter disclosed enormous development of the musculature (fig. 3). The mucosal and submucosal layers were thinned. Inflammatory reaction was practically absent.

Fig. 4 (case 3).—Cross-section of the right ureter taken from the dilated portion at the same level of the ureter as that in figure 3. There was no muscular hypertrophy, but evidence of inflammation may be noted; × 105.

Sections from the unobstructed right ureter contained muscle that stained poorly, and gave evidence of marked infiltration, with grouped and scattered small round cells and polymorphonuclear leukocytes. In portions, the submucosa appeared edematous. There was no increase of connective tissue in sections of the narrow portion of the right ureter seen in the pyelogram. It is probably more correct to regard such a portion as one in which dilatation had not taken place rather than as a region of stricture.

The different characteristics of these two ureters must indicate a difference in the etiology of the dilatation. On the left was enormous, smooth dilatation, without evidence of infection of the ureter and with marked hypertrophy of ureteral

musculature. At the ureteral orifice was definite cause for obstruction. On the right was a dilatation of more modest extent, and with irregularity of outline. There was no obstruction and in the ureteral wall no muscular hypertrophy, but there were marked inflammatory changes (fig. 4). It was concluded that this was dilatation due to inflammation of the ureteral wall.

CASE 4.—*Infection, the cause of dilated calices.*

A man, aged 75, died of sarcoma of the right axilla with metastasis. Occasional nocturia during the last four years was the only urinary symptom. The urine had contained occasional erythrocytes and pus cells.

At necropsy, very slight enlargement of the prostate gland, of the median bar type, was found. Postmortem pyelograms disclosed apparent clubbing of all calices, without dilatation of the ureters. The capacity of the right pelvis and ureter was 17 cc., and that of the left pelvis and ureter, 15.5 cc. On opening each pelvis, severe inflammation was evident. The ureters gave no evidence of infection, either grossly or microscopically. Inflammation appeared to be the sole cause of the dilatation of these calices. The bladder was normal and gave no evidence of having been seriously obstructed by the prostate gland.

CASE 5.—*Ureteral inflammation.*

A man, aged 62, had been under observation for five years because of diabetes and associated cystitis. Four large vesical diverticula, which did not empty, were known to be present. Five years previously a stone had been removed from the lower part of the left ureter, after four weeks of symptoms. Death resulted from acute renal infection two weeks after the development of symptoms.

At necropsy, left pyonephrosis, with atrophy of the kidney, was noted; the kidney weighed only 100 Gm. The right kidney weighed 250 Gm. Both ureters were dilated, tortuous, sacculated throughout and kinked secondarily. The diameter of the left ureter varied from 3.3 to 12.6 mm., and that of the right ureter, from 3.3 to 8 mm. A small, contracted bladder with severe cystitis and diverticulitis was noted. There were marked injection of the mucosa and some thickening of the ureters and pelves.

Microscopic sections of both ureters disclosed dilated blood vessels, many young connective tissue cells and much infiltration with inflammatory cells. There was no evidence of obstruction of these ureters. There was no trace in the ureter of the former ureterolithotomy. The prostate gland was small, and there had been no obstructive vesical symptoms.

In the absence of obstruction it seems that dilatation of these ureters must have resulted from ascending infection of the ureteral wall with resultant atony.

COMMENT

From analysis of the foregoing cases it seems evident that inflammation is not an uncommon factor in ureteral dilatation. It often acts as a contributory cause, and it may be, in the absence of mechanical obstruction, the only factor in the dilatation. The effect of inflammation on the ureter is conceivably one of interference with function and atony of the ureteral wall, lessening the resistance of the ureter to pressure from within. The dilatation of inflammation has certain characteristics. It is irregular, giving an irregular ureterographic outline. It never reaches the large size often seen with obstruction. The microscopic picture is one of inflammation rather than one of muscular hypertrophy, as is often the case in obstructive dilatation.

That ureteral dilatation always accompanies pregnancy seems to be an established fact. It is generally assumed that the dilatation is due to mechanical obstruction, although the precise manner in which it occurs is not yet clear. Of interest in this connection in this series were two deaths occurring during pregnancy, one in the fourth month and one in the second month. Marked ureteral dilatation was noted in the first case, whereas in the second the ureters were normal grossly and microscopically. It is conceivable that the uterus in the latter case had not reached sufficient size to cause pressure at the pelvic brim, if there is anything in the hypothesis that such pressure causes dilatation.

That the dilatation of pregnancy does not always persist is evident from the fact that in this series six multiparas who had been pregnant from three to eight times had ureters and pelves which were normal grossly and microscopically.

Five multiparas in this series had dilated ureters. Chronic inflammatory changes were evident in the ureters of four on microscopic examination. It seems, then, that the inflammatory changes had prevented the return of the ureter to normal. In the fifth case, in which the ureters were without inflammatory change, a neurogenic origin of the dilatation could not be ruled out.

Many explanations have been offered as to the mechanism of the ureteral dilatation which occurs with prostatic hypertrophy. The truth probably is that no explanation will suffice for all cases.

That it was not due to distortion or kinking of the lower end of the ureter by the enlarged gland was exemplified in case 1. Interference with ureteral emptying by hypertrophy of the vesical wall does not seem a satisfactory explanation (case 1). There were seven cases in which hypertrophy of the vesical wall was marked and in which there was no ureteral dilatation. In two cases in which the vesical wall was thinner than usual the ureters were dilated.

There were twenty-nine cases of prostatic hypertrophy in this series. In twenty of these there was no ureteral dilatation. These ureters were microscopically free from inflammation except in one case, in which acute pyelonephritis was terminal. From the character of the dilatation in certain cases, it is a fair conclusion that inflammation was at least a contributory cause, either by its effect on the ureteral valve or by causing atony of the wall of the ureter.

SUMMARY AND CONCLUSIONS

The diameters of normal ureters may vary within wide limits, both at the widest and at the narrowest points.

The capacity of the normal ureter and pelvis in adults was found to vary from 4.5 to 20 cc. An unusual case in which the capacity was 30 cc. was found.

Ureteral stricture of intrinsic inflammatory origin was not found in this study.

Ureteral spasm may occur soon after death and be evident in postmortem pyelograms.

Dilatation of the ureter can result from inflammation of the wall of the ureter in the absence of mechanical obstruction. Such dilatation presents anatomic and clinical characteristics.

Involvement of the lower part of the ureter in pelvic inflammation, by interfering with ureteral function, may cause dilatation of the upper part of the ureter and renal pelvis, without actual obstruction.

Chronic ureteritis will cause the ureteral dilatation that occurs in pregnancy to persist.

The ureteral dilatation associated with prostatic hypertrophy may have an obstructive cause, although the mechanism is as yet not clear. Ureteral inflammation is frequently a contributing factor and may be the only factor.

CHROMATOPHORE (MYO-EPITHELIAL) TUMORS OF THE MAMMARY GLAND

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For more than twenty years I have been acutely sensible of the fact that certain globular cancers of the breast present a particularly bad prognosis. In addition to their external form, they present a varied histologic structure which requires the assumption of a wide latitude of cell metaplasia to keep them within the group of epithelial tumors.

Recently I encountered a patient whose tumor seemed to be a connecting link between the aforementioned group and the intracanalicular fibro-adenomas. As the cells of this tumor seemed to spring from its subepithelial cells, I am calling growths of this type chromatophore tumors, realizing that this is little more than a symbol. Since they do not produce pigment, one cannot call them melanomas, though they duplicate the histologic structure of the pigmented tumors in a striking manner. Amelanotic melanomas would be a more accurate though cumbersome designation.

The use of a term suggesting pigment-producing potentials has a justification in that morphologically the subepithelial cells can be traced from the surface skin down the ducts for varying distances. The epithelium of intracanalicular fibro-adenomas is composed of several layers, and though the lower layer cannot be morphologically proved to have a relationship with the chromatophores of the skin, the clinical course warrants consideration of the possibility of such a relationship. Since so little is known morphologically of chromatophore cells, the failure to demonstrate them about the ducts can have little weight. Perhaps those sufficiently skilled in microtechnic may be able to add something to the knowledge concerning the nature of the subepithelial cells found about the ducts and in the epithelial layers of these tumors. The term "myo-epithelium" has been applied to certain subepithelial cells. Though it is sanctioned by high authority, it seems to assume a hybrid among cells.

At any rate, "myo-epithelium" suggests nothing to the surgeon, while "chromoma" at once calls up the picture I desired to present. Not only does the life history of this tumor resemble the chromomas, but the histologic structure as well closely resembles the varying picture seen in chromomas.

Most surgeons, I believe, are now in the habit of regarding pigmented tumors as forming a class of their own. Certainly nothing in the pathologic literature is more confusing than the attempts which have been made by pathologists to place the pigment-bearing tumors now with the sarcomas and now with the epitheliomas, neither of which they resemble either in morphology or clinical course.

The patient was 49 years of age when she first noticed a tumor in her breast. She had been conscious of its presence for only three months. I believe this observation was correct, for I removed a goiter from her seven years before which resulted in myxedema. In order to study this condition she was kept under close observation, and no tumor was discovered in previous examinations. When she presented herself on Jan. 16, 1931, she had a tumor which was globular, slightly bosselated, densely elastic and freely movable without any attachment at any point.

Fig. 1.—Tumor obtained at the first operation, natural size. Somewhat irregularly spheroidal, it shows slight lobulations with several small cysts. The generally pale pinkish surface is traversed by paler fibrous bands.

It lacked none of the clinical signs of an intracanalicular fibro-adenoma except its appearance late in life and its apparently rapid development.

The first operation, which consisted in the resection of that part of the breast which harbored the tumor, was done on January 17. The tumor, on section, showed indefinite lobulations with here and there small cysts in an otherwise pinkish-white surface (fig. 1). A diagnosis of intracanalicular fibro-adenoma was made in the operating room with but slight misgiving.

The patient returned on September 14, with a large recurrence, and a complete mastectomy was done. The cut surface of this new tumor showed marked cystic formation with a pinkish-white border of varying thickness. The solid part contained some areas of blood infiltration. The tumor still bore gross relations to the intracanalicular fibro-adenomas (fig. 2). The protrusions in the cystic portion were distinctly intracanalicular.

On December 11, the patient returned with a renewed recurrence, which was represented by a number of distinct tumors, of well defined globular outline, movable against their environment and independent of each other. They lacked the

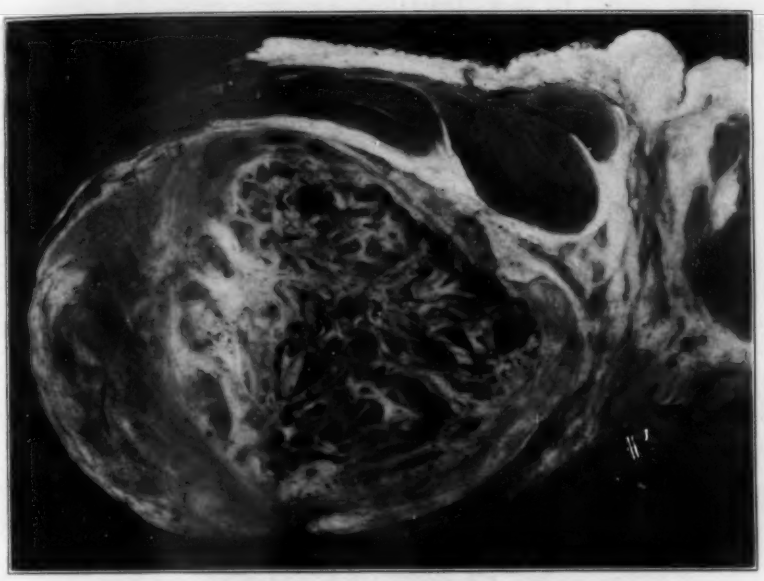

Fig. 2.—Tumor obtained at the second operation, natural size. The left half is made up of pinkish-white areas with here and there some hemorrhagic areas. The right half is made up of a cystic area with trabeculated walls.

Fig. 3.—Second recurrence, natural size. Four distinct tumors, generally expansile in growth, are in evidence. They still retain evidence of the cyst and lobule formation which characterized the primary growth.

hard feel characteristic of epithelial malignant recurrences. On section, these tumors showed a paler pink surface than the preceding recurrence, but were still cystic in parts (fig. 3). The impression these tumors gave on clinical examination, and likewise on section, was that of a recurrent amelanotic melanoma as one sees this in recurrences in tumors of the skin.

The tumor quickly returned, and the patient died on April 19, 1932, fifteen months after the first operation. There was marked local destruction (fig. 4), with extensive metastasis in the axillary and mediastinal lymph glands as well as in the lungs. In the local destruction of tissue as well as in the site and manner of invasion the tumor simulated certain melanotic tumors. The autopsy was done by Dr. C. Alexander Hellwig, who supplied the photograph and tissue.

Histologically, the most interesting phase was the apparent beginning of the malignant growth from cells lying beneath the surface epithelium of the intracanalicular papillations (fig. 5*A*). The part of the primary tumor not involved in the malignant growth was for the most part myxoid in structure with areas

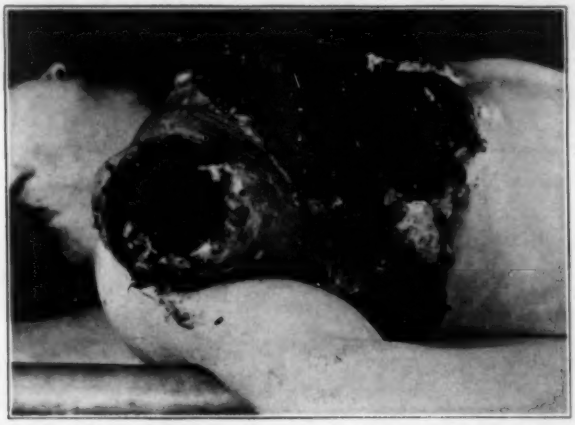

Fig. 4.—Appearance of the tumor area after death. The extensive invasion which the tumor had made is in evidence.

of distinct lipoid structure. The epithelium of the growth was untouched both in the original tumor (fig. 5*B*) and in the recurrences (fig. 6). In the primary tumor the cells were spindleform or ovoid. As the rate of growth increased, the cells became more globular and resembled fully the cell forms in the most rapidly growing melanotic tumors. The protoplasm was more or less drawn into prolongations and in most areas presented a poorly staining intercellular stroma (fig. 7). The more rapid the growth, the more irregular the cells became. In the rapidly developing parts of the tumor, cells formed about the lumen of a vessel just as one sees them do in rapidly growing teratomas, as in those of the kidneys and testicles.

Of great interest to me is the fact that a number of eminent pathologists who examined slides from these tumors varied widely in their opinions as to the nature of the growth. These opinions varied from a belief that the growth was unquestioned sarcoma to a belief that it was carcinoma with pronounced metaplasia. When pathologists dis-

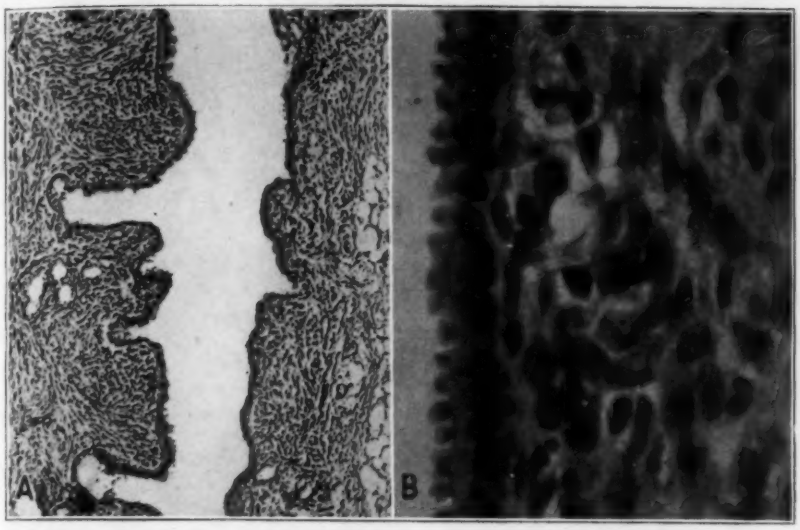

Fig. 5.—Slide from the primary tumor. In *A*, the cells are most numerous just beneath the epithelium. At a greater depth the cells become more spindle-form. In *B*, a high power magnification, the epithelium is shown intact. Beneath the epithelium, the cells are seen to contain large nuclei with many granules.

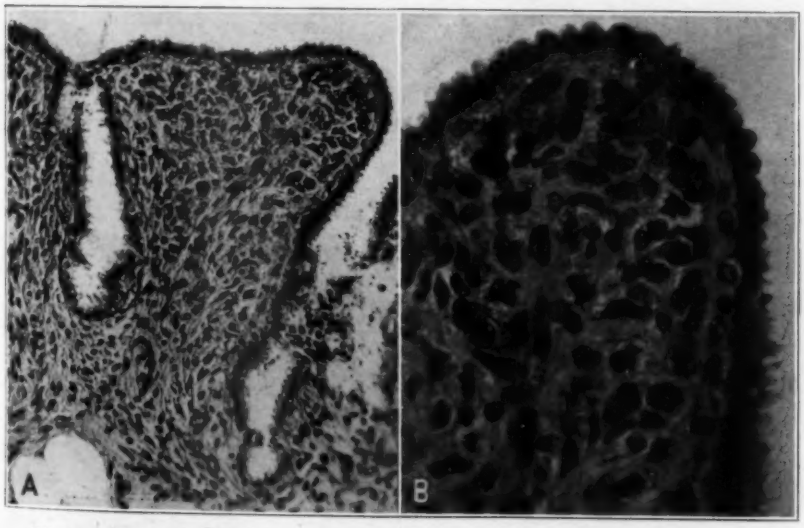

Fig. 6.—Slide from the second recurrence. In *A*, the cells are larger and more deeply staining than in the preceding figure. The surface epithelium forms an untouched and unbroken layer. In *B*, high power magnification, the cells are shown with large granular nuclei.

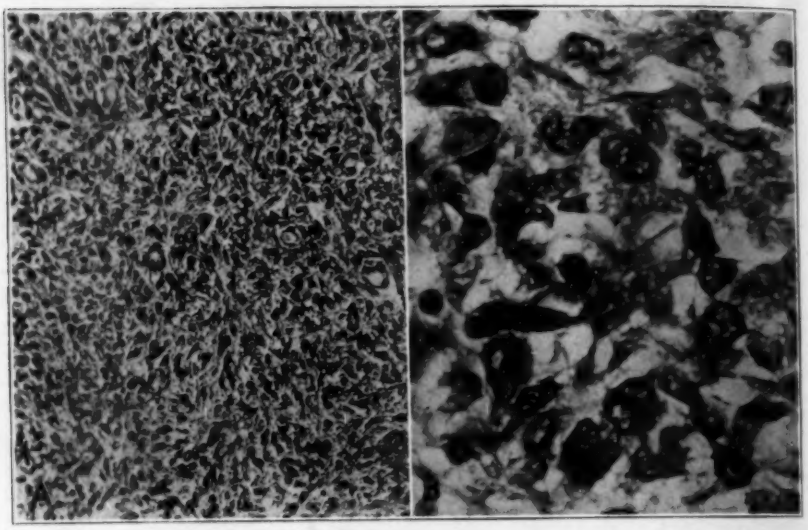

Fig. 7.—Slide from the second recurrence. In *A*, the entire field is made up of a homogeneous cell mass with relatively few small vessels. In *B*, high power magnification, are shown cells of varying forms but the main type is constant.

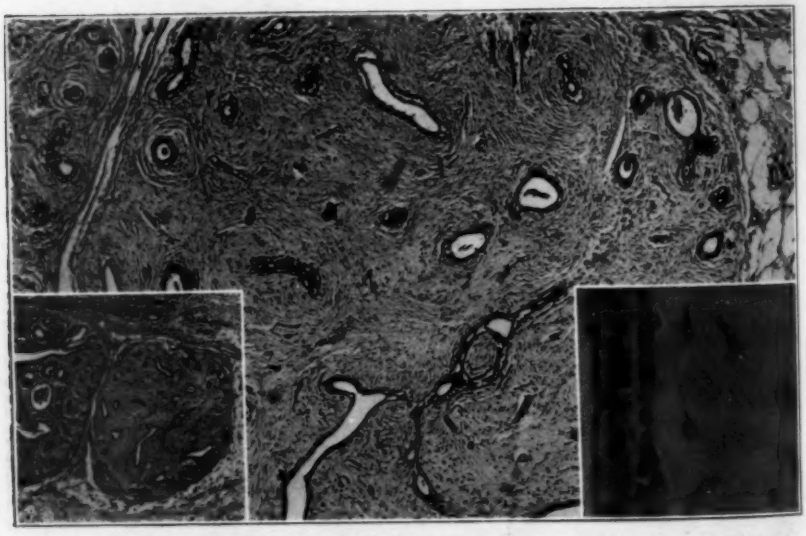

Fig. 8.—Slide from a tiny fibro-epithelioma. The structure is that of larger tumors of this group. The distinct encapsulation of the tumor is shown at the left. The left insert shows the tumor in low magnification; the right, a high power magnification of the epithelium.

agree on the histologic nature of a tumor group, the surgeon is warranted in adopting a classification based on clinical observation which will be useful to him.

As this tumor in its life history reproduces so perfectly, both in its gross manifestations and in its histologic structure, the rapidly growing melanomas of the skin, the provisional classification of this tumor with the melanomas seems to be warranted.[1]

INTRACANALICULAR FIBRO-ADENOMAS

It seems justifiable to interpolate here some observations on the genesis of intracanalicular fibro-adenomas which I have been able to

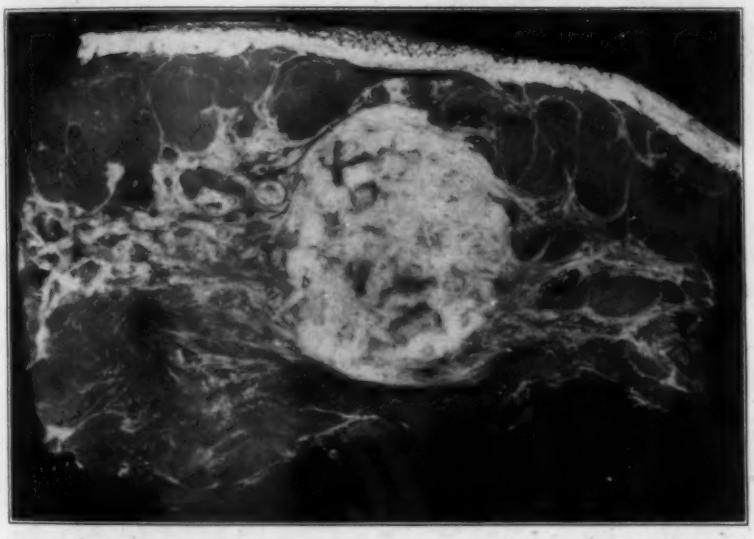

Fig. 9.—Cross-section of a tumor of the breast, showing pseudo-encapsulation and lobular structure in parts of the tumor.

make in the past. For this purpose the smallest tumors should be selected.

The notable feature is that tumors scarcely larger than a pin's head have the characteristics of large tumors (fig. 8). The epithelium is composed of several layers. The high power photomicrograph (fig. 8, right insert) shows the double layer of cells. It is the lower of these layers from which the tumor here discussed seems to grow.

It is noteworthy that these tiny tumors are perfectly encapsulated and are independent of any other changes in the mammary gland. They

1. This judgment is based on previous studies made on chromomas: Ann. Surg. **60**:89 (July) 1914; **87**:99 (Jan.) 1928; Surgical Pathology of the Skin, Philadelphia, J. B. Lippincott Company, 1931, p. 145.

are found incidentally now and then in the study of normal mammae. It is as near the truth as one can come to assume that in the development of the duct a disturbance in the anlage has occurred, that these tumors represent, in fact, a disturbance in the primary development of

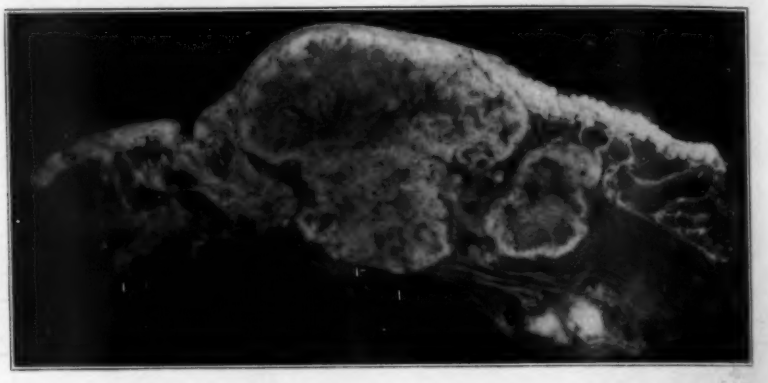

Fig. 10.—Cross-section of recurrence. The tumors are surrounded by a pseudocapsule. The surface shows lobulations with areas tending to cyst formation.

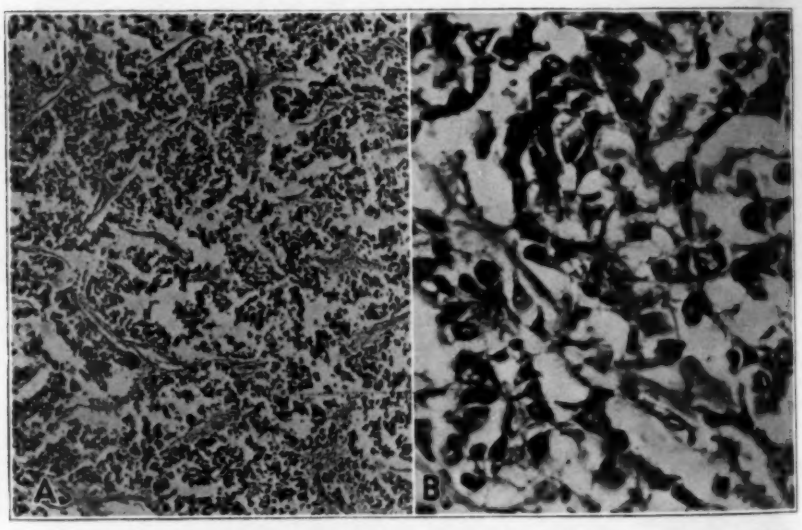

Fig. 11.—Slide from the tumor in figure 10. In *A*, the section is very cellular with irregularly placed stroma. In *B*, the cells vary in size, shape and tinctorial reaction. The stroma is fibroma-like.

the gland. It is not without interest that in the rapidly growing parts of these tumors areas were found which resembled those found in accepted teratomas. The occurrence in the terminal duct is assumed, for in some of them acinus-like areas are found in conjunction with areas showing distinct duct formation.

The case reported here somewhat in detail seems to suggest the possible nature of other spheroidal tumors of the breast which are less obviously related to primary benign tumors, but which run a similar clinical course. They are distinctly spheroidal, suggest an expansile growth by their pseudo-encapsulation, recur as distinct globular tumors, likewise expansile in growth, and are equally vicious in their clinical course. Several such examples may be briefly presented:

A woman, aged 64, first noted a lump in her breast six weeks before consulting a physician. Attention was attracted to the breast because of a slight pain. Four weeks later she had a severe pain in the armpit. A firm tumor the size of an egg, which the patient had not discovered, was palpable in the outer upper quadrant of

Fig. 12.—Cross-section of a large pseudo-encapsulated tumor of the breast with lobulation and cyst formation.

the left breast. Large glands were palpable in the axilla. Radical operation was performed.

On section, the tumor was seen to be spheroidal with a well marked pseudocapsule in some areas. The pale pink surface showed pseudolobulations (fig. 9).

Eight months after operation the growth recurred. It was removed (fig. 10). The main tumor was the size of a lemon, and there was a smaller one the size of a walnut. The cut surfaces presented the same picture as the primary tumor. Both had a pseudocapsule.

The microscopic structure was cellular, resembling that of a seminoma of the testis (fig. 11 *A*). The cells were irregular in size, form and staining reaction (fig. 11 *B*). There was some fibrin-like intercellular stroma. Rapidly growing melanotic tumors, particularly in the young, sometimes show a similar structure.

A woman, aged 51, a year before she sought medical advice noticed a mammary tumor the size of a marble. A spheroidal slightly bosselated hard tumor the size

of an orange was palpable. The skin was attached to the tumor, but there was no dimpling or retraction of the nipple. The cross-section showed a pseudo-encapsulated tumor, the surface of which showed indications of lobulation and in parts a tendency to cyst formation (fig. 12).

The slide showed spheroidal masses of cells with degenerated areas between them. The cells were of varying size, as were the nuclei. The striking feature was the large number of cells with a large amount of clear cytoplasm. These suggested the clear cells sometimes seen in the ducts of normal breasts.

The structure of the last mentioned tumor resembled that in the first case. Its origin from a primarily benign tumor cannot be proved, but when first discovered the patient compared it in size and shape to a marble. The tumor resembled that in the first case to such a degree that such a possibility must be entertained.

It has been my experience that the malignant tumors of the mammary gland which possess a pseudocapsule, in whole or in part, always terminate fatally within a year or two, no matter how soon after the discovery of the tumor operation is performed, or what the extent of the operation, or whether or not there are palpable metastases. These tumors occur in women at the menopause or beyond that period. I have not observed them in younger women. My youngest patient, operated on some twenty years ago, was 46 years of age.

There is a group of tumors which begin within the acini and in which the cells are loosely joined and diffusely scattered. Some of these appear as though they might have arisen from the subepithelial cells, but instead of growing away from the lumen of the acini they grow into it. At any rate, many of these tumors are globular, though they do not develop a pseudocapsule, and their course is usually malignant.

CONCLUSIONS

1. Intracanalicular fibro-adenomas may give rise to malignant tumors which spring from the subepithelial layer.

2. They run a course parallel with that of the chromatophore tumors in the skin.

3. Globular pseudo-encapsulated cancers of undemonstrable origin run a similar clinical course.

4. These tumors like melanotic tumors do not cause metastases to the bone.

A NEW METHOD OF RECONSTRUCTION OF THE LIP

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AND
GERALD BROWN O'CONNOR, M.D.
SAN FRANCISCO

Successful reconstruction of a lip is a difficult and intriguing problem. The addition of a new operation to the remarkably long list of operations proposed in the past can be justified only if the new procedure proves to possess added advantages and fewer disadvantages than its predecessors. In reviewing the literature, about sixty-five different methods for this operation were discovered, and this new procedure is described because it possesses the advantages of simplicity, cosmetic fidelity to the normal in its results, noninterference with muscle and nerve supply and production of nearly normal function, and is applicable to restoration of either the upper or the lower lip.

Before this problem can be successfully adjudged, its factors must be analyzed, and the obvious first step is a review of the anatomic structures about the mouth together with their physiologic action. Of these structures, the musculature is the most pertinent to our problem. The motor innervation and the blood supply are next in importance. The following is a description taken from Deaver's "Surgical Anatomy." [1]

The muscles of the mouth are the orbicularis oris, the levator labii superioris, the levator anguli oris, the zygomaticus major, the zygomaticus minor, the buccinator, the risorius, the depressor labii inferioris, the depressor anguli oris and the levator labii inferioris.

The orbicularis oris muscle (sphincter oris), nearly an inch in breadth, surrounds the mouth, forming a sphincter; at its periphery it unites with several muscles which act upon that aperture. It consists of two parts—an inner, central, or labial part, and an outer peripheral, or facial part; the two differing in appearance and in the arrangement of fibers, like the orbicularis palpebrarum muscle. The inner, central, or labial portion consists of pale, thin fibers, fine in texture, corresponds in position with the red margin of the lips, and has no bony attachment, but is continuous around the angles of the mouth from one lip to the other. The outer, peripheral, or facial part is thinner and wider than the labial, and has a bony attachment as well as connection with the adjacent muscles. In the upper lip

Read before the annual meeting of the California Medical Association, Pasadena, May 2, 1932.

1. Deaver: Surgical Anatomy, Philadelphia, P. Blakiston's Son & Co., 1901, vol. 1, pp. 498 and 499.

the orbicularis oris muscle is attached at each side of the middle line to the lower part of the septum nasi by the naso-labial slips, and to the alveolar border of the upper jaw opposite the incisor teeth; in the lower lip it is attached to the alveolar border of the lower jaw opposite the canine teeth by a single fasciculus (musculi incisivi). The cutaneous surface of the muscle is intimately connected with the skin of the lips and surrounding parts. The intimacy of this union is so great in some instances that the mouth is surrounded by radiating wrinkles, especially marked in the upper lips of women. The labial integument of the male probably

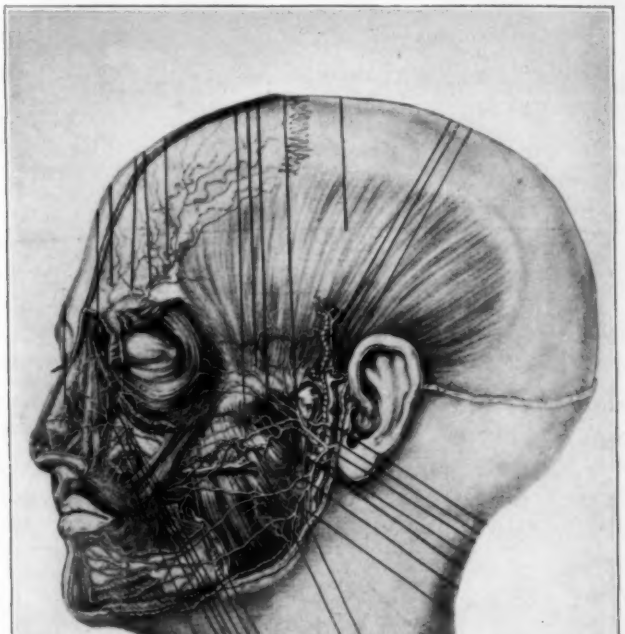

Fig. 1.—Anatomy of the face. Note the musculature and the nerve supply about the mouth. (From Deaver: Surgical Anatomy, Philadelphia, P. Blakiston's Son & Co., 1901.)

contains fewer wrinkles on account of the presence of large hair bulbs. The deep surface of the orbicularis oris is covered by mucous membrane, between which and the muscle, in the submucous tissue, are the coronary arteries and the labial glands.

Nerve Supply.—From the buccal and supra-maxillary branches of the cervico-facial division of the facial nerve.

Action.—When the facial and labial portions act conjointly, they press together and project the lips. The labial fibers acting alone bring the lips and the angles

of the mouth together and invert the lips. The facial fibers acting alone press the lips against the alveolar borders of the jaws, and, at the same time, evert the lips. The orbicularis oris is the antagonist of all those muscles which converge to the lips from the various parts of the face.

Of prime importance is the orbicularis oris with its sphincter action. All the other muscles about the mouth are opposed to this muscle. This sphincter action must be kept constantly in mind together with the axiom that a sphincter cut at one point still functions as a sphincter, but cut at more than one point, loses its function.

One only too frequently notes in examining patients for whom reconstruction of the lower lip has been done (usually after the removal of a new growth) that the new lip is short and tense and the upper lip is forced into protrusion; indeed, there is almost a Gumpian expression. Functionally, such a lip is a constant distress, for there is usually continual drooling of saliva, and clarity of speech is markedly disturbed. It is most difficult for these people to sound *b, f, m, p, v, w, ph,* and *wh.* The great number of operations devised for the repair of the lip indicates that no method gives completely satisfactory results. Indeed, many methods fall far short of even a reasonable repair.

REVIEW OF OPERATIVE METHODS

A study of these many operations is illuminating for the development of rationale of procedure, and in many cases the factors contributing to the failure to approach good cosmetic and functional results are obvious.

Among the early operations, Chopart, in 1785, designed an advancing flap from the chin by carrying parallel incisions downward to the neck, making a square flap pedicled below. This flap was undermined and advanced upward to fill the defect. The first and most obvious criticism of this method is that no epithelial lining has been provided for the oral side of the flap. The sine qua non of reconstruction involving any body cavity is that an epithelial lining as well as covering must be provided. Alquié, in 1855, modified Chopart's operation by adding flaps of mucous membrane from the cheeks. Other disadvantages are the tendency of the flap to be pulled down and to contract; also muscular control is limited, and the nerve supply to the muscles of the lower lip is cut. Serre used horizontal advancing flaps, one from each cheek, but this resulted in a short tight lip. Zeiss employed double vertical flaps pedicled below. Lisfranc devised an operation with a median line vertical incision and two lateral incisions, and Sédillot used lateral incisions with supplementary incisions into the upper lip to allow a borrowing of tissue to form the angles of the mouth. Beau made two outward and downward curving incisions from a central point and rotated the flaps upward.

Weber employed horizontal overlapping flaps below the defect, and the flaps were then slid one upon the other so that the tip of one flap approximated the base of the other. Dieffenbach and also Adelmann used lateral angled flaps. Juselre and also Reid carried their incisions from the angles of the mouth outward and downward and then rotated the flaps inward. Pollosson's operation and Berger's were similar in the use of lateral horizontal incisions and shifting flaps. Nélaton and Ombrédanne devised a bold procedure. An incision was carried back from the angle of the mouth to the ear and thence downward and for-

Fig. 2.—Advancing type of flaps.

Fig. 3.—Advancing overlapping type of flaps.

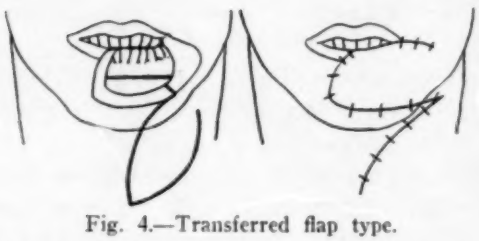

Fig. 4.—Transferred flap type.

ward beneath the mandible. The cheek was taken full thickness to the anterior border of the masseter muscle and subcutaneously thence to the ear. The whole flap was moved medially to fill the defect. Auger used a large, low and lateral pedicled flap, and Ledrau and Berg used smaller single inferior lateral shifting flaps. Viguine-Morgan, Wölfler, Mazzoni and others employed a large double pedicled flap embracing most of the lower part of the face and chin.

A number of surgeons conceived the principle of the use of a buttress of tissue on the chin to support the newly formed lower lip. In this manner, Sédillot turned two symmetrical vertical flaps pedicled above and buttressed them on the chin. Lallemand's operation consisted of a

transposed flap taken low down and pedicled at the side, and this plan followed Langenbeck, both using buttress tissue on the chin. Landreau used a single recurving flap. The Trélat and Buchanan and Syme's operations employed lateral advancing flaps but left a portion of chin tissue for buttress. Morestin's operation swung up a double pedicled flap from beneath the chin to rest on the normally anchored tissue. Grant extended long incisions outward from the angles of the mouth, dissected the upper flaps free and swung them to the midline. Larger's operation commanded considerable attention in the employment of an advancing flap including the outer third of one side of the upper lip and extending out into the cheek. Bruns swung down two full thickness ascending lateral flaps. Watts reported a reconstruction of the lower lip with a flap from the arm, the raw surface of which had been grafted and healed before the transfer of the flap. This has the disadvantage of skin of different color and texture and the discomfort of having the arm maintained against the face for a period of two weeks.

Fig. 5.—Buttress type of operation.

Hoffmann, Morestin, Evans, Duformentel, de Francesco, von Mutschenbacker and Twyman offer various types of advancing flaps. Joseph uses rotating pedicled flaps. Tzaïco brings up long cervical reverse flaps from the midline, while Sebileau employs temporal pedicle flaps. Esser devised an operation with ascending triangular pedicles which were brought down and fitted to form a quadrilateral, and he has also introduced a bold figure 3 incision, which involves most of the cheek and upper half of the neck, and which is rotated into the defect.

Sir Harold Gillies, in his war reconstruction work, designed numerous ascending and descending flaps, and his results were uniformly the best of all those reviewed. Pickerill favors a temporal pedicle flap joined to a neck flap for lining and thence referred to the defect.

A review of all these operations demands a measurement of each by the yardsticks of simplicity, conservation, function and cosmetic result, for too many of the plans fall short on one or more counts. Analysis and criticism again demand reference to the basic anatomy and physiology of the part. Advancing flaps are only occasionally used in modern reconstruction surgery on account of the tension and the distortion produced. They are not adequate, and experience teaches that they almost always fall short of producing even a fairly good result.

This point is stressed now with especial emphasis, because books on surgery are replete with diagrams of many varieties of flaps for the correction of defects of the lips and show handsomely completed operations (diagrammatically) as cosmetically perfect. This we know to be scarcely possible from trial and from logical deduction based on the fundamentals.

The older methods nearly all failed to provide an epithelial lining, but in recent years no operation is planned without strict attention to this factor. A common fault of most operators, unless they have been trained in reconstruction surgery, is to underestimate persistently the size of the defect to be repaired and to fail in judgment of the amount of tissue requisite to accomplish the repair, or to be too sanguine of the possibility that the flap may be properly mobilized for the consummation of the transfer. These difficulties constantly menace such plastic procedures and give added strength to the plea for simplicity of plan. Then, too, a properly planned operation will obviate the terrific and unnatural distortion of the donor part which follows the adoption of many of the reviewed recommendations, for lack of balance of facial contour is certain to result in dismay for the surgeon and dissatisfaction on the part of the patient. Once again, the object of the operation is not merely the closure of a defect, but in addition the satisfaction of all the foregoing factors.

Further, judgment dictates due regard for normal lines of tension of the skin, and this Larger has shown graphically in his diagrams of his lines of tension. A study of these diagrams will reveal the fact that flaps can be selected to fall within these lines and that failure to do this militates against the best results. Hunt quoted Larger in his statement, "If due regard is shown for these lines and incisions are made in their direction, inconspicuous scarring is usually the result. Any incision made at right angles to these lines, however, results in scar formation." In addition, if the natural grooves are followed, the scarring is even more inconspicuous. A contemplation of these factors suggests the nasolabial groove as the optimum site for the appropriation of tissue.

Distortion of the mouth after reconstruction by many of the methods enumerated is strikingly evident. This is true especially of flaps taken from one side, because such technic creates marked tension on one side as against relaxation on the other with consequent unbalancing of the facial contour. Moreover, there may be added to this distortion the atony and sagging caused by severed muscles or by lost motor nerve supply to the muscles of that side. Other methods of this type cause a shortening of the oral commissure on the side of the flap. This lack of symmetry gives the patient an unnatural and bizarre expression. Advancing flaps are especially undesirable, as they not only distort the surrounding tissue but furnish insufficient material for a full everted

lip and consistently produce the shortness and tenseness which mars the completed reconstruction. The short, tight lower lip not only commonly causes drooling but also an abnormal protrusion of the upper lip beyond the lower and interferes seriously with the clarity of speech.

A selection of flaps through the full thickness of the face is a grave mistake. If such a plan is adopted, the incisions are made through the integrity of the sphincter of the mouth, thus destroying all possibility of proper function. Inclusion of this transposed muscle, while technically completing the normal constituents of the lip, defeats the functional power of the part. Only recently the fallacy that inert muscle can be of functional value was illustrated by the report of a case in which a strip of sternomastoid muscle was utilized and implanted into the reconstructed lip.

Again, scrutiny of the anatomy of the face will recall that innervation of the muscles about the mouth is derived from the branches of the facial nerve. Diagrammatically, the branch to the muscles of the upper part of the mouth come from the nerve trunk which crosses the face approximately in a line from the lobe of the ear to the middle of the upper lip. The muscles of the lower lip and chin are innervated by a branch extending approximately in a line from the lobe of the ear to the middle of the chin. It is therefore evident that many of the flaps suggested not only will destroy the integrity of the indispensable facial musculature but will render the remaining musculature impotent by the destruction of its motor stimulus.

Profiting by the careful analysis of all the factors of the problem of reconstruction of the lips and forewarned by the unsound theories of such reconstruction which have resulted unsatisfactorily, we offer the following operation as a basic procedure for the reconstruction of either the upper or the lower lip. This operation possesses the necessary qualifications before mentioned of simplicity, cosmetic fidelity to the normal in its results, production of nearly normal function and noninterference with muscle and nerve supply.

TECHNIC

The principle of the operation is the use of two full length opposed ascending flaps placed in the nasolabial groove. The technic of the operation is shown in the accompanying diagrams and pictures of the patient before and after operation. These flaps consist of skin and subcutaneous tissue only, and at no point is any part of the musculature or its motor nerve supply severed. The nasolabial groove was selected as the donor site, because scarring there is inconspicuous and especially because this region provides a sufficient supply of facial tissue which is relatively free from hair. Furthermore, this tissue will be the same color and texture as the normal lip, which is a strong argument for its use, rather than flaps taken from distant parts. The skin of the face is distinctly different in texture and color from that of any other part of the body. Flaps taken from the arm and chest stand out with startling prominence on account of these differences,

and while such flaps may furnish sufficiency of normal tissue, the cosmetic result is not pleasing. It will be seen that our flaps are placed according to the principles of "Langer's lines of tension." The flap from one side is brought down and reversed to form the lining of the lip in such a manner that the skin surface is toward the mouth and the raw surface is directly outward. It is then sutured into position after splitting the margin of the defect so that raw surface will come in contact with raw surface, and the skin surface of the flap will be in continuity with the mucous membrane of the mouth. The opposing flap is then brought down to furnish the covering and is sutured raw surface to raw surface and the lining flap sutured to the free skin edge of the facial wound.

Mindful of the principle of the sphincter action of the M. orbicularis oris, these opposing flaps form the bridge between the two ends of the severed orbicularis oris muscle and reconstitute its function as a sphincter muscle. The adoption of this principle obviates the necessity of the employment of any transplant musculature, as it performs better in this manner than with the unnatural function of a transposed muscle or uninnervated muscle. All the opposing muscles may act normally as they are anchored into the base of the new lip.

The blood supply is naturally adapted to these flaps, as the bases of the flaps lie over the facial arteries with their coronary branches, and thus the vitality of the flaps is almost certainly assured.

In the illustrated operation, when these flaps were brought down into position, as shown in the accompanying photographs, smaller flaps of mucous membrane were taken from the lateral borders of the defect and blended into the superior border of the sutured flaps in such a manner as to form the angles of the mouth and a goodly portion of the vermilion border of the lip. These mucous membrane flaps were carried upward, so that their bases approximated the normal angles of the mouth. A further transposition of mucous membrane from the upper lip was planned to complete the vermilion border of the lower lip, but, as was noted by Sir Harold Gillies in his reconstruction work during the war, flaps of skin turned into the mouth were found to take on the appearance and characteristics of mucous membrane. We found that the remainder of the border of the skin forming the upper margin of the lip and not covered by mucous membrane took on these characteristics to such a degree that a well developed simulation of the normal vermilion border took place and close examination is required before the difference can be detected. Such transplantation of mucous membrane is relatively easily effected. The patient is thoroughly satisfied with the appearance of the lip and does not wish to have further transposition of the mucous membrane done.

After two weeks the bases of the pedicles are returned, and then a period of from two to three months should elapse before final retouching of the newly formed lip is done. These long full length flaps have an added advantage as they do away with all the troubles which come from the joining of bilateral flaps in the midline, at which point the suture line is apt to break down and contraction is apt to occur; also the scar at this point is a cosmetic disfigurement. Minimal scars on the face will be noted in the accompanying photographs of the finished case, as these photographic prints are from unretouched negatives made by us. A further advantage of the full length flap is the certainty of sufficiency of tissue since the defect can be accurately measured and the flaps appropriately fashioned. Sufficiency of tissue avoids the too common short and tense reconstructed lip.

The criticism might be voiced that this method is not readily applicable for immediate repair of a lip defect (as following the removal of the part on account of a new growth). It is true that the repair is better done after healing is complete than when attempted with the tissue

Fig 6.—The flaps are outlined.

Fig. 7.—One flap is brought down and reversed to form the lining.

Fig. 8.—The other flap is brought down to form the covering.

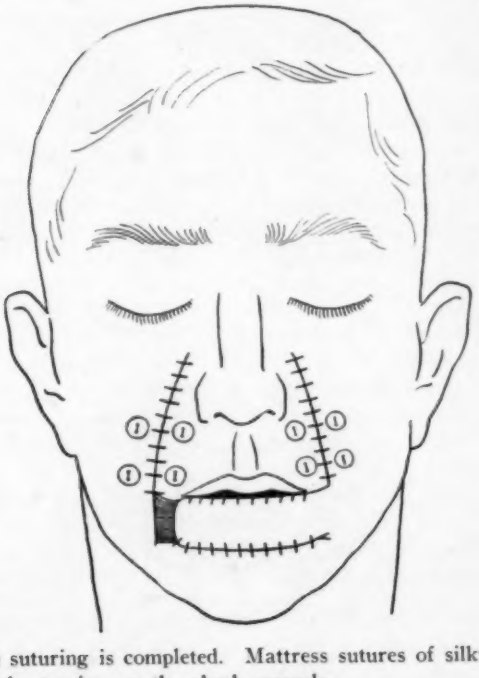

Fig. 9.—The suturing is completed. Mattress sutures of silkworm gut through buttons relieve the tension on the cheek wounds.

in the region of the bases of the pedicles in an edematous and perhaps infected state. Such a condition would jeopardize the blood supply of the flaps by the mechanical effect of pressure and by favoring thrombosis of the vessels. It is far better to allow the patient the discomfort of a few weeks or months without a lip than to sentence him to a lifetime of discomfort and social limitation by the over-zealous efforts to "fill the gap." Then, too, surgical judgment dictates a waiting period after removal of new growth tissue until a reasonable certainty exists that there will be no recurrence of the tumor.

The cosmetic result can be judged by the reader. Special attention is called to the ease of closure of the mouth and to the profile views

Fig. 10.—Condition of the patient before operation.

with the normal-appearing groove between the chin and lower lip. There may be a few hairs on the base of the inturned flap, but these can be readily and permanently removed by the electric needle. Attention is also called to the photographs illustrating the function and ease with which the patient opens his mouth and shows his teeth. The action of showing the teeth indicates efficient anchorage of the radiating opposing muscles. In the last picture the patient is shown whistling, an accomplishment with the new lip which he has only recently developed, following the gradual softening of the transplanted tissues. This illustrates the sphincter action obtained in the orbicularis oris muscle and the soundness of the principle of bridging the divided ends of this muscle.

REPORT OF A CASE

H. W., was first seen by us on Jan. 27, 1930. His complaint was total loss of the lower lip from cancer. The full history is not given, since the salient features are the only ones germane to this paper. The patient was 47 years of age at the time of his first visit and had always been in good health with the exception of measles at the age of 9 years, to which there were no sequelae.

Seven years before we saw him he noted a "crack" in the mucous membrane of the lower lip. This persisted, but finally healed, then broke open several times. A "lump" eventually developed at the site of the "crack," and this was treated by roentgen rays. The tumor did not disappear and was excised surgically in November, 1928. Microscopic examination of the tissue revealed basal cell epithelioma. The tumor recurred and was removed by electrocautery on Jan. 17, 1929.

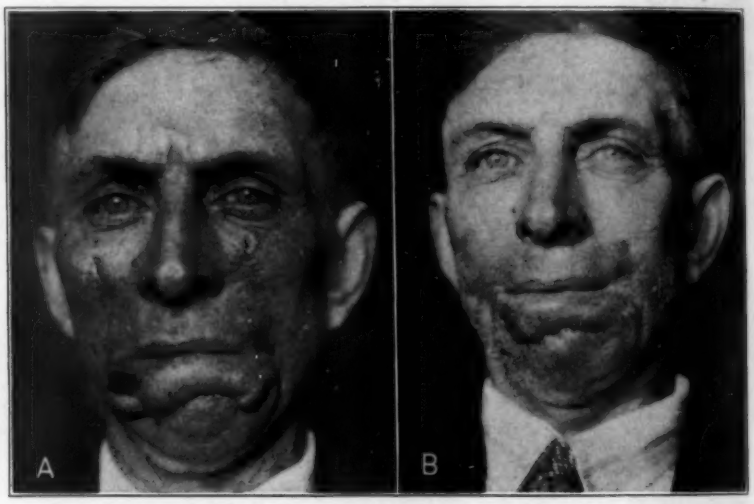

Fig. 11.—*A*, condition of the patient after healing of the transposed flaps. *B*, the bases of the pedicles are returned; the suture material is in situ.

The patient had been a heavy smoker, using a pipe and cigarets.

When we saw him first on Jan. 27, 1930, he presented a complete loss of the lower lip. No induration was present, and no glands were palpable in the neck. The wound had been healed one year. The Wassermann test in the blood was negative. His condition on his first visit is shown in figure 10.

Reconstruction was started on March 21, 1930. At the first operation, which was done with the patient under ether anesthesia, the ascending flaps were fashioned (fig. 6), brought down and sutured into the defect, after splitting the margins of the defect. The lining flap was placed skin surface in, as shown in figure 7, and the covering flap was brought over as in figure 8. Small flaps of mucous membrane were turned up from the lateral borders of the defect to form the angles of the mouth. Mattress sutures of silkworm gut, passed through buttons, relieved tension on the skin of the cheek wound, and the completed operation is shown in figure 9. Horsehair was used for skin closure. The healed condition of this stage is shown in figure 11 *A*. Readjustment of the pedicle bases was done April 10, 1930, under

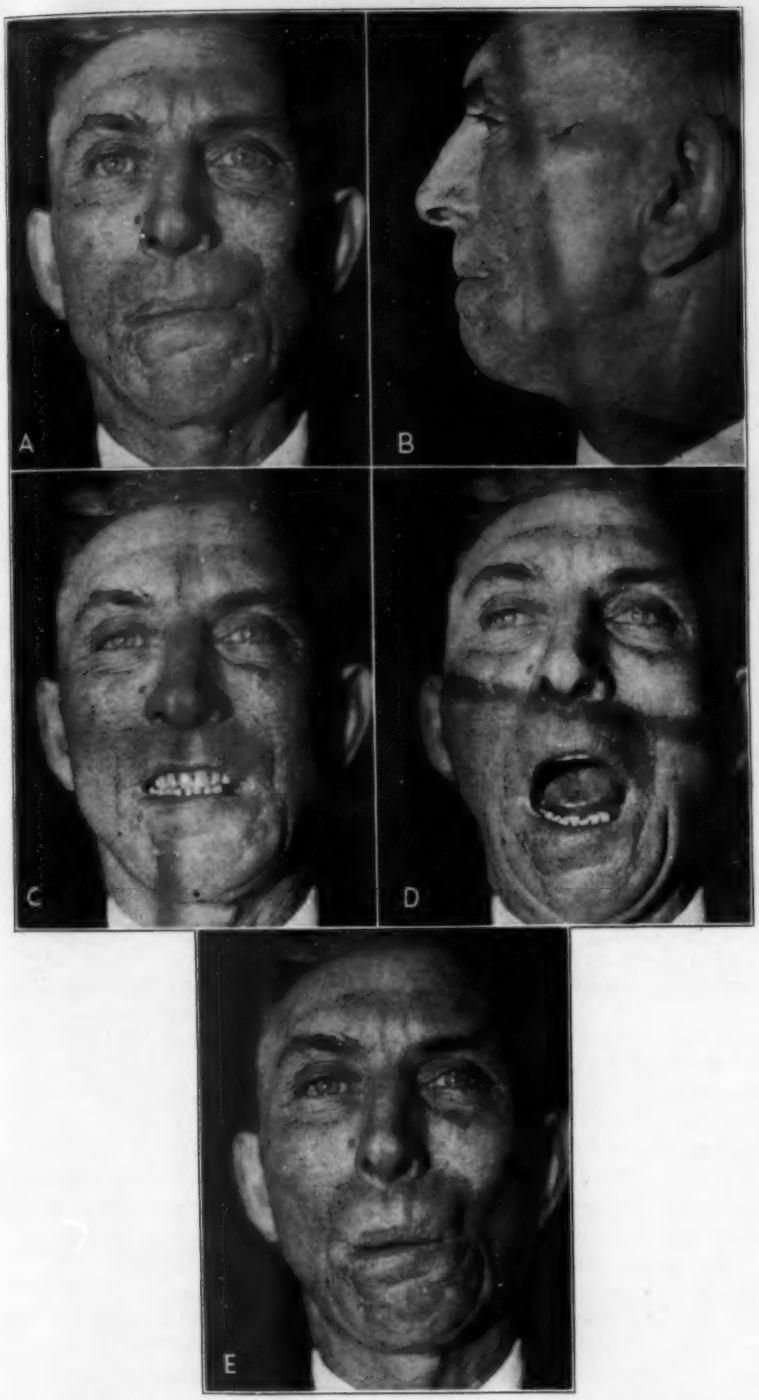

Fig. 12.—*A*, the result of the operation. There is no distortion of the lip or face. *B*, the profile view shows the full contour of the reconstructed lip and the normal approximation with the upper lip. *C*, note the action of the radiating muscles opposing the M. orbicularis oris. *D*, the ease of opening the mouth is shown. *E*, the patient is shown whistling. This illustrates the action of the orbicularis oris muscle through the bridge of the transplanted flaps.

local anesthesia, procaine hydrochloride 1.5 per cent, and the result is shown with the suture material in situ in figure 11 *B*. Two small readjustments have been made since then, and the final result is shown in figure 12.

CONCLUSION

We must return to the statement of requirements laid down in the first paragraph and measure the result obtained in this case by the yardsticks of the declared essentials. Thus:

1. Simplicity. Few operations of this type offer as simple technic, and this simplicity is evident from the drawings.

2. Cosmetic fidelity to normal. We would be rash indeed to compare our results to Nature's handiwork, but we surely should not cease in our attempts to duplicate her art, and a reference to the photographs will show that the contours of the reconstructed lip do approach the outlines of the normal.

3. Noninterference with muscle and nerve supply. It is evident that there is no interference with either muscle or nerve supply, as the flaps are taken through skin and superficial fascia only.

4. Near normal function. Again we cannot duplicate Nature, but the final photographs do show that, for the ordinary movements, this lip is a functional entity.

5. The method is applicable to restoration of either the upper or the lower lip. The upper lip may be constructed in this manner by planning the bases of the flaps to lie at a point in a line with the proposed lip.

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CHYLE CYSTS OF THE MESENTERY

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Porter [1] presented the subject of chyle cysts of the mesentery before the Western Surgical Association twenty-six years ago. He reported a case of his own and discussed 20 cases, reports of which had appeared in the literature. He regarded the chyle cyst as a surgical rarity, and believed that it was less common than the serous mesenteric cyst. On examining the records of autopsies at the University of Minnesota recently, we found that in approximately 15,000 autopsies no case of chyle cyst had been recorded. In a search of the clinical records of St. Luke's and of St. Mary's hospitals, Duluth, representing a total of over 200,000 cases, we found that but 2 cases of chyle cyst had been recorded. In the Los Angeles General Hospital, according to Alesen,[2] no such case was recorded from 1912 to 1929.

Friend [3] assembled 52 instances from 1875 to 1912; Benedict [4] included Friend's list and collected a total of 96. Flynn regarded mesenteric tumors as among the rarest of those in the abdomen. The consensus of these men seems to be that approximately 200 cases might be found in medical literature.

REPORT OF CASES

The 2 cases we wish to report are as follows:

CASE 1.—A boy, aged 4, was referred to one of us by Dr. Grover on Dec. 5, 1930. Two years before the child had been operated on for appendicitis, but drainage had not been employed. The symptoms at that time were similar to those for which the child was referred. The present attack began with acute pain at about 2 o'clock in the morning of December 4. The mother gave an enema with some result, and the child vomited. A second enema, because of the continuance of pain, brought no result. She called her physician on December 5. The history of appendectomy and the nature of the symptoms prompted the physician to suspect intestinal obstruction, and he sent the boy to the hospital, where Dr. Doolittle saw him in consultation. The following report was made: The leg was flexed,

1. Porter, M. F.: Chylous Cysts of the Mesentery, Tr. West. S. A., 1905, p. 242.

2. Alesen, L. A.: Chylous Cyst of the Mesentery, California & West. Med. **30**:261 (April) 1928.

3. Friend, E.: Mesenteric Chyle Cyst, Surg., Gynec. & Obst. **15**:1 (July) 1912.

4. Benedict, A. L.: Bibliography of Chylous Cyst of the Mesentery, Surg., Gynec. & Obst. **16**:606 (June) 1913.

and the facies anxious. There were dark circles under the eyes. The tongue was dry and coated, and the breath fetid; the tonsils were clean but red; there was no postnasal exudation. The ear drums showed some luster. There was slight enlargement of the glands. The lungs were normal, and no murmurs were heard in the heart. The pulse was 100 and regular, and the temperature, 101 F. The abdomen was slightly distended (oval) with slight definite fulness in the extreme lower right quadrant. Marked tenderness and spasm were noted over the entire abdomen, with the maximal findings over the lower portion of the right side of the abdomen, which was too tense for one to palpate any

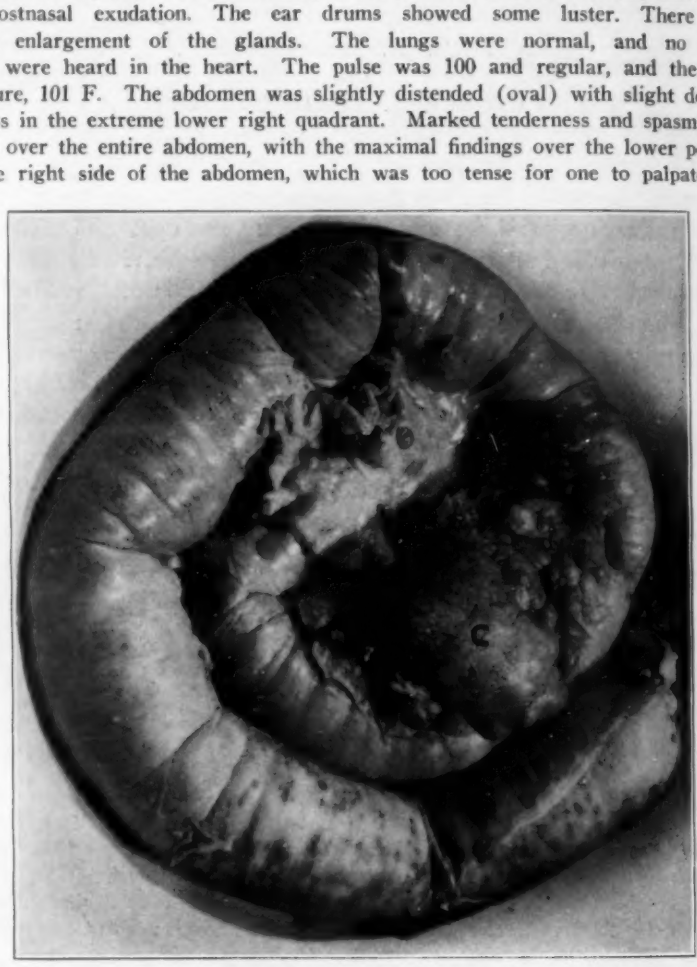

Fig. 1.—Specimen photographed a few hours after autopsy. *C* is the largest of the cysts. Other smaller cysts are grouped around the intestinal margin.

masses. There were no lumbar spasms. Definite flatness was noted over the hypogastric and iliac regions, and there was considerable pain in the abdomen at times.

Rectal examination revealed some indurated bogginess of tissue in the lower portion of the right side of the abdomen. No definite accumulating mass was felt. The hemoglobin was 85 per cent; the red cell count, 4,580,000; the white cell count, 25,900, and polymorphonuclears, 92 per cent. Roentgen examination with an enema of barium sulphate under fluoroscopic control showed that the opaque solution passed all the way up the colon and into the terminal ileum. There was no roentgen evidence of diverticuli, a new growth or intussusception. With the

history of the sudden onset of the attack of abdominal pain and vomiting and in consideration of the foregoing findings, operation was advised at once but no definite diagnosis was made.

When the abdomen was opened, a milky, odorless fluid escaped from the peritoneum. A hard nodular mass was found below the level of the umbilicus, semilunar in shape and running transversely in the lower portion of the abdomen. The mass was delivered and found to be in the mesentery of the small intestine. It consisted of small, pure white masses, some clear cystic masses and several apparently hemorrhagic ones. The total mass was so extensive, involving so much of the

Fig. 2.—Specimen showing the opposite side from that in figure 1.

mesentery, that no attempt at resection was made. Smears and culture were taken at the time. These showed diplococci and were reported later as pneumococci. The boy lived four days; extreme distention developed, and he died of peritonitis.

Autopsy, which was performed a few hours after death, showed: (1) chylangioma of the mesentery with formation of multiple cysts, (2) status after an old appendectomy, (3) pneumococcus peritonitis, (4) edema and congestion of the lungs, (5) beginning bronchopneumonia of the right lung and (6) status after a recent laparotomy (exploratory).

The upper loop of the intestine was extremely distended, measuring up to 14 cm. in circumference (fig. 1). The serosa of the distended intestine was congested

Fig. 3.—Microscopic section from the cystic area: *A*, thin-walled dilated lymphatic spaces; *B*, larger lymphatic with thin layer of the fibrous connective tissue beneath the lining epithelium; *C*, clumps of lymphocytes and coagulated albuminous material.

and showed numerous small hemorrhages. There were no signs of mechanical obstruction of the intestine. Superficial ulcerations of the valvulae conniventes of the small intestine were seen. It was noted that there were no dilated chyliferous vessels in the serosa of the small intestine or in the mucosa, not even in that segment connected with the cystic mesentery. The retroperitoneal glands were somewhat edematous. The thoracic duct was of normal size and contained a small amount of slightly cloudy fluid. The part of the mesentery showing the cystic changes corresponded to a loop of the small intestine 10 inches (25.4 cm.) in length and beginning about 2 feet (60.96 cm.) below the end of the duodenum (fig. 2). Here the mesentery was thickened and showed cystic formations, some watery in appearance, some bluish and some milky. A few of the cysts contained hemorrhagic serous fluid. The largest of the cysts measured 8 by 4.5 by 3.4 cm. This was irregular in shape and was multiloculated. There were numerous other cysts measuring from 1.5 to 2.6 cm. in diameter, and many much smaller. Some of the cysts near the margin of the small intestine involved the serous and muscular coats of the small intestine. When the mass had been cut through, the cut section gave a cavernous appearance. Some of the cystic nodules which had a more compact consistence showed on the cut surface cavernous spaces filled with clotted blood (fig. 3). Small lymphatic glands and lymphatic nodules included in the tissue between the dilated lymph spaces showed moderate dilatation of their sinuses, especially of their peripheral sinuses. These dilated sinuses contained lymphocytic cells and larger mononucleated cells. Small lymph glands taken from the involved mesentery showed similar changes, while glands from the mesentery farther away showed a more normal condition. No truly solid tumor mass could be found. An irregular network of whitish channels of varying thickness was seen in places; these were filled with milky fluid. One larger cystic space near the root of the mesentery contained more compact fatty masses resembling caseated material but more whitish. Microscopically, this was formed chiefly of fat droplets of irregular sizes. Smears from the peritoneal exudate showed pneumococci.

The second case we are recording through the courtesy of Dr. W. A. Coventry, who collaborated with the late Dr. T. R. Martin in its study. This case was more chronic.

Case 2.—A woman, aged 48, for five months complained of burning in the epigastrium and vomiting after meals which sometimes caused her to leave the table. She felt better if she kept very quiet and also if the stomach was empty. The appetite was poor, but the bowel movements were regular and at times a little loose. She tired easily and complained of nervous chills. She had had one stillborn child seven years before. She stated that she had always had "weak blood." There was a past history of typhoid. She was a frail, thin woman, weighing 95 pounds (43.1 Kg.). Her blood pressure registered 150 systolic and 90 diastolic. The hemoglobin was 46 and the red cell count, 3,880,000. The temperature was 98.2 F. The urine was normal. The Wassermann reaction of the blood was negative. In the lower left abdominal quadrant close to the abdominal wall was felt a tumor the size of a chicken egg. The enema of barium sulphate gave negative results except that pulling on the tumor seemed to drag the sigmoid with it. The diagnostic impression was that the condition was either a tumor of the sigmoid or an enlarged mesenteric gland.

At operation Dr. Coventry found a large number of tumors in the mesentery of the small intestine running up to the root. Some of these appeared caseous and some cystic. Some were as large as an egg. The involvement was too great for resection. The patient failed and died on the seventeenth day. At autopsy, numerous thin-walled and thick-walled cystic tumors, the size of an English walnut and smaller, were found at the base of the mesentery.

A larger tumor measuring 8 by 8 cm. in diameter was found; it was composed of a conglomeration of mesenteric and peritoneal lymph glands. Several cystic tumors were in intimate contact with the wall of the intestine and were apparently connected with the subserous, dilated, chylous vessels of the small intestine. The large tumors at the base of the mesentery were surrounded by an edematous area. Some cavities were filled with puslike greenish-yellow material. The walls of these were especially edematous. The mesenteric glands were edematous throughout and were often connected more or less intimately with the cystic formations. The small intestine was irregularly dilated. The wall of the small intestine was irregularly thickened in places. The serosa was much thickened and was congested, and a few dilated and distended subserous chylous vessels could be seen. The mucosa of the small intestine was edematous in places and showed numerous small hemorrhages. Here and there, small chylous cysts could be seen. The small intestine could not be separated from the mesentery without opening of several of the cysts described. The thoracic part of the thoracic duct was slightly dilated and filled with a watery content. The larger lymphatics along the primary iliac vessels were slightly dilated. The cisterna chyli was involved in the tumors formed by the conglomerated glands at the base of the mesentery and could not be found.

Microscopic examination showed the largest gland at the base of the mesentery to contain in its cavity many leukocytic cells, lymphatic cells, a fibrinous network and very numerous, often intracellular fat droplets of varying size. The wall of the cavity was formed by granulation tissue with many fibroblasts and plasma cells; the fibroblasts were often loaded with fat droplets. In the wall of the cavity the lymphadenoid tissue was still well preserved, and some of the dilated sinuses were filled with desquamated endothelial cells loaded with fat granules. Other cysts showed the same structure. The wall of the cyst was formed by connective tissue, which was infiltrated with many lymphocytic cells.

COMMENT

Friend,[3] in 1912, studied a group of 52 cases and found that these cysts may occur at any age from early childhood to late in life. There is no particular age at which one may look for them. He, and also Benedict,[4] found that males and females may have the condition in about equal proportions. In Benedict's group of cases the youngest patient was 5 weeks old, and in Friend's group the oldest patient was 80 years old. Flynn was inclined to believe that these cysts occur more commonly in the third decade.

We have tabulated 16 cases reported in recent literature in which more elaborate histories and detailed findings are obtainable. The various periods of time during which the complaints prevailed, with the number of cases in each instance, were as follows: 12 years, 1 case; 6 years, 1 case; 4 years, 1 case; 3 years, 1 case; 2 years, 4 cases; 1 year,

2 cases; 5 months, 1 case; 4 months, 1 case; 2 months, 2 cases; 3 days, 1 case, and 8 hours, 1 case.

SYMPTOMATOLOGY

From the foregoing figures it will be seen that in 14 of the 16 cases there have been from two months to twelve years during which the patients have been more or less ill, complaining and affording an opportunity for diagnosis. Some of these complaints include malaise, loss of strength, loss of weight, easy fatigability, feeling of nausea, occasional vomiting, abdominal pain to varying degrees from a dull ache to spells of greater severity, and a palpable tumor in half of the cases. Two patients had abdominal distention for one year, and another patient for six months. There was abdominal tenderness in 12 cases. This was usually generalized over the abdomen but often localized at the umbilicus, to the right or in the lower portion of the abdomen. Rigidity occurred in the acute cases. The white cell count, which was stated in 9 cases, was above 10,000 in 8 cases and was over 20,000 in 4 cases.

DIAGNOSIS

Flynn and Swartley made the observation that a correct diagnosis had not been made before operation or autopsy. This observation is borne out in the recent group of 16 cases that we have tabulated. A mesenteric tumor was, however, suggested in the diagnosis on two occasions. There is no grouping of symptoms characteristic of this disease. The acute cases usually suggest intestinal obstruction or peritonitis. Rupture of a cyst and immediate pain, nausea and vomiting in a woman would suggest ruptured tubal pregnancy. The long-standing cases have no characteristic diagnostic features. The abdominal tumor, if single, is smooth and rounded, and fluctuation can usually be made out. It does not move with respiration. The tumor, if multilocular, as in our case 1, may have an irregular or nodular feel. A tumor in the mesentery should be freely movable, often excessively so, both in vertical and horizontal directions, and moving it may cause pain. The point of attachment may be approximately located, usually quite centrally in the abdomen. The patient may find relief by turning and lying in certain positions, as on the side, with extreme flexion of the hip and knee joints, a point mentioned by Freudenthal.[5] A long-standing history, not paralleled by wasting, may rule out a malignant growth. As chylous ascites has been encountered with more or less frequency at operation, it would seem that diagnostic puncture or tapping would lead to valuable information. The enema of barium sulphate is of value in ruling out involvement of the colon. Screening

5. Freudenthal, P.: Chylous Cyst of the Mesentery, Hospitalstid. **71**:353 (April 12) 1928.

of the stomach, used by Joyce and co-workers,[6] may show a pressure defect. Pneumoperitoneum with screening or with the roentgenogram has been suggested by Flynn as offering possibilities in the determination of the presence and location of the cyst. Differentiation must be made from fluctuant masses in the omentum, from the pancreas, and from ovarian cysts, retroperitoneal tumors and lipoma.

ETIOLOGY

Klemm found the wall of a true cyst to arise from mesoderm, and he believed, therefore, that such cysts are of embryonic origin. Kauff-

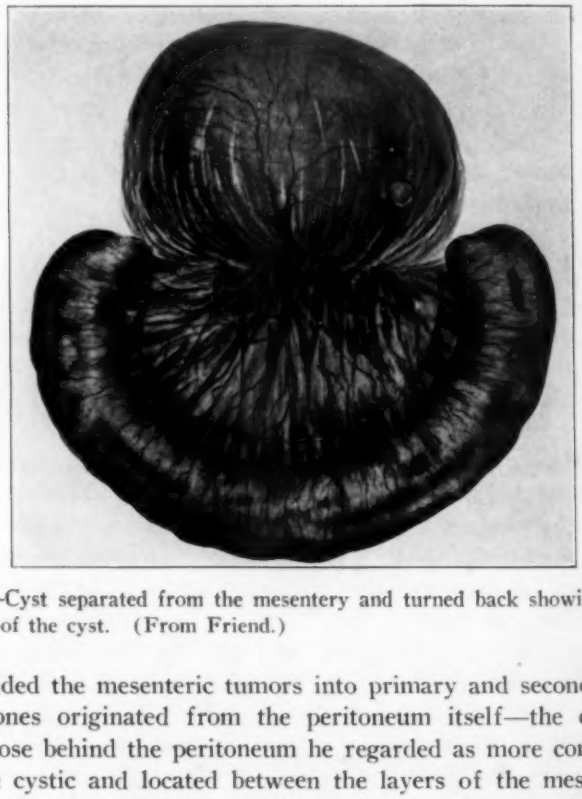

Fig. 4.—Cyst separated from the mesentery and turned back showing a nodule in the wall of the cyst. (From Friend.)

mann divided the mesenteric tumors into primary and secondary. The primary ones originated from the peritoneum itself—the endothelial type. Those behind the peritoneum he regarded as more common. If they were cystic and located between the layers of the mesentery, he regarded them as lymphangiomatous or as lymphangiocavernous tumors. The cystic mesenteric tumors may contain chyle, in which case they are called chylangiomas. They may be single or multilocular. Most of them are found in the mesentery of the small intestine, usually in the mesentery of the ileum. Cystic degeneration of the lymph gland is especially mentioned as the causative factor in the

6. Joyce, T. M.; Howard, M. A., and Fitzgibbon, J. H.: Chylous Cyst of the Mesentery, Northwest Med. **29**:123 (March) 1930.

origin of the cyst. It may be tuberculous as a result of tuberculous ulcers of the intestine, or it may result from a temporary blocking of the gland and degeneration following enteritis or some other inflammatory process, as appendicitis. Friend showed, in illustration of his article, the wall of a cyst in which a nodule at the side and intimately a part of the wall seems to be the original gland from which the cyst developed (fig. 4). In our case 2 the largest gland at the base of the mesentery contained in its cavity many leukocytic cells, lymphatic cells, a fibrinous network and very numerous, often intracellular, fat droplets of varying sizes. In Freudenthal's case, the opinion, on microscopic examination, was that a cystic degeneration of the lymph gland was the causative factor.

TREATMENT

Surgical treatment offers the only hope of cure. Several different methods of attack have been used. Porter, in his series of 20 cases, found that operation was performed in 14 and that in 6 the condition was discovered at autopsy. Of the 14 patients operated on, 3 died. Of those who had had an excision or enucleation of the cyst, 6 recovered and 2 died. When incision and suture of the sac to the abdominal wound was done, there were 5 recoveries. In 1 case in which excision of the cyst, mesentery and part of the bowel was done, death ensued. The mortality in the 16 cases of our tabulation, all methods of treatment included, was 25 per cent. Friend mentioned 25 cases in which incision and drainage were done with a mortality of 8 per cent and 18 cases in which extirpation was done with a mortality of 33.3 per cent. Begouin found that sewing of the sac to the abdominal wall, to be opened later, resulted in a mortality of 7.5 per cent. This was a better showing than that in a series of 60 cases in which extirpation was done. He collected reports of 54 cases in which puncture and aspiration were done without a fatality. Flynn, in 1912, resected the tumor and 40 inches (101.6 cm.) of bowel in a girl of 16 and obtained a recovery. Wilson [7] emptied the cyst found in a boy of 8 years, with recovery of the patient, but felt at the time of his report that the cyst was refilling. Alesen [2] excised the cyst in a girl of 5 and obtained a recovery. Benedict [4] stated that while all the patients on whom marsupialization was performed recovered, the deaths after extirpation or enucleation seemed to be due to primitive surgical methods, intestinal occlusion, peritonitis and other serious complications rather than to the method chosen. Modern surgical technic and preoperative preparation may serve in future cases to bear out this statement. The available methods therefore have been: (1) aspiration, (2) incision

7. Wilson, G. I.: Mesenteric Chylous Cysts, Brit. M. J. **1**:102 (Jan. 19) 1929.

and drainage, (3) enucleation and (4) marsupialization. Intestinal resection and extirpation will probably always carry a higher mortality. The choice of method should be made to fit the case.

SUMMARY

1. While mesenteric cysts were mentioned as far back as 1620, Rokitansky is credited with the first description of chyle cysts in 1842. Porter,[1] Friend,[3] Benedict [4] and Flynn have reported groups or reviews of cases, all of which have been considered in the present study. Chyle cysts of the mesentery are not common; indeed, they are relatively rare and have been encountered at all ages from early childhood to old age. In this paper a report of 2 cases has been added to the literature of the subject, and an attempt has been made to summarize the various symptoms that occurred in the reported cases. An effort has also been made to present the clinical features that may assist in leading to a diagnosis, a point which has been extremely baffling in the past.

2. From two months to twelve years elapsed in 14 of 16 cases during which time the patients were complaining and affording an opportunity for diagnosis.

3. Abdominal distention of greater or less degree was found in 10 of 16 cases.

4. A freely movable tumor in the lower part of the abdomen which fluctuates and has a midline attachment should suggest mesenteric cyst.

5. The discovery of chylous ascites by exploratory puncture may assist in establishing a differential diagnosis.

6. Marsupialization has resulted in the largest number of recoveries.

EXPERIMENTAL TRANSPLANTATION OF THE PANCREAS INTO THE STOMACH

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While the extensive investigative work on the pancreas proves that this gland is an essential organ in the human economy, the literature concerning surgical procedures on the pancreas is scanty and loosely scattered through medical journals and textbooks. The information that we gained from a search of the literature particularly impressed us with the fact that the present knowledge of diseases of the pancreas and the practical application of surgical treatment to the cure of these conditions are hardly any further advanced today than they were fifty years ago, when surgical treatment was limited to a few operations performed for the cure of retention cysts by excision or for the formation of an external fistula. Since that time a great deal of experimental work has been done in attempts to clear up the mysteries surrounding the function of the pancreas.

On the clinical side, Friederich (1878) summarized the meager knowledge of pancreatic disease that was available in his time. On the surgical side, it was not until the era of antiseptic and aseptic surgery and the consequent safe exploration of the abdomen that animal experimentation could be undertaken with hope of success and the pathology of the gland could be studied in the living human being.

Since Lister, physiology and surgery have developed hand in hand. Senn published his paper, "Surgery of the Pancreas," in 1885, and Fitz (1889) laid the foundation of the present knowledge of acute pancreatitis. Körte (1898), Oser (1898), Opie (1903), Robson (1907), Coffey (1909), Macleod, Banting and Best (1922) and de Takats (1930) are but a few of the prominent ones among an army of workers on

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the subject who approached the diagnosis and treatment of pancreatic disease from the basis of anatomy, pathology and physiology—the only proper and scientific basis.

In experimenting with the pancreas, because of its very nature—the unusual composite, complicated functions, the intimate relationship to other abdominal structures and the difficulty of surgical approach—one meets with many problems the importance of which is equaled only by their difficulty of solution. Every such difficulty encountered has impeded not only the clinician in his diagnosis and therapy, but also the surgeon in his technical mastery of the surgical problem.

In 1909, Coffey published a preliminary report entitled "Pancreato-Enterostomy and Pancreatectomy." His originality and the apparent delicacy of the technic he developed in completing his work were indeed a great inspiration to us; however, in performing his operation for pancreato-enterostomy, one of us met with little success. Coffey took a loop of bowel, the adjacent sides of which he sewed together. He then made an opening into the loop in the same way as Finney opens the duodenum and stomach in his operation for ulcer. Into this opening Coffey transplanted the pancreas. He stated that it made no difference which end of the sectioned pancreas was implanted, the current would flow normally or in reverse and discharge into the intestine.

Perhaps it was the technical difficulties of this operation that prevented its success. At any rate, we decided to perform similar experiments, using the stomach instead of the jejunum. At first we did not pay much attention to the study of the subject from the standpoint of physiology, our wish being to know whether in case of necessity this could be accomplished without bad effects on the animal. In this experiment we used seventy-two dogs. The object was to devise by direct surgical attack a rational method of treatment in certain cases of injury involving either the tail or the head of the pancreas, and of early tumor growth involving the head. In performing these operations, two essential points were constantly kept in mind: first, avoidance of leakage of the pancreatic fluid; second, the surgical disposal of the severed or injured end in such manner that both the internal and the external functions of the gland would be preserved.

We soon learned that the dog's pancreas is easily injured. The gland is better protected when not handled with any kind of instrument. The pancreas in the dog differs from the human pancreas in being covered with peritoneum. While this condition renders its implantation into the stomach a safer procedure, our first experiments failed because of leakage and peritonitis.

The surgical reasons for using the stomach instead of the jejunum were its accessibility, its favorably large size and the elimination of

any possible obstruction of the lumen of the bowel or strangulation of the gland, which might occur if it were implanted into the small intestine.

SERIES I

The first experiment consisted in making a pocket between the muscularis and the mucous coat on the posterior wall of the stomach (fig. 1). An inch and a half (3.77 cm.) of the distal end of the pancreas was removed entirely, and then the cut surface of the remainder was implanted into this pocket and held in place by a piece of silk tied around the end of the pancreas and fastened to the wall of the stomach at the bottom of the pocket (fig. 1 *B*). This kept the cut end of the pancreas anchored while two interrupted sutures were taken at the entrance on each side of the pocket in order to promote healing and to prevent leakage of the pancreatic fluid. Four weeks after the operation the dog was killed. A study

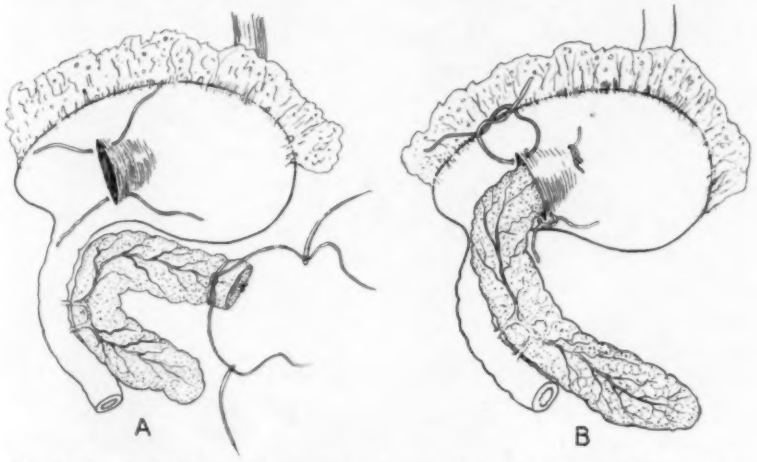

Fig. 1.—Implantation of the pancreas into a pocket in the wall of the stomach in series I: *A*, a pocket is made under the muscular coat in the posterior wall of the stomach. Sutures are placed in the stomach and pancreas. *B*, the cut end of the pancreas is sutured into the pocket in the stomach, preventing the discharge of pancreatic juice into the peritoneal cavity.

of the results of the operation revealed a firm, smooth union between the tail of the pancreas and the wall of the stomach. The pancreas was in a good state of preservation. There was no accumulation of pancreatic juice in the pocket nor any erosion (digestion) of the walls of the pocket.

A second experiment consisted in the removal of the tail of the pancreas for about 3 inches (7.6 cm.); the cut end of the pancreas was drawn into the stomach through a crucial incision, and the opening was closed around it (fig. 2). A study of the results of the operation (six to ten weeks later) revealed firm, smooth union between the pancreas and the wall of the stomach. The pancreas looked normal. Serial sections were taken about 25 microns apart throughout the entire area of contact of the pancreas with the stomach, and it was found that the mucosa of the stomach had completely grown over the defect produced at operation, and that there was a layer of connective tissue between the mucosa of the stomach and

the pancreatic tissue. The foregoing experiment was repeated in other dogs with this difference, that the main pancreatic duct was exposed and divided between ligatures. In these dogs, also, the mucosa was found to have united over the cut end of the pancreas. Presumably, the pancreas emptied itself into the duodenum by accessory ducts.

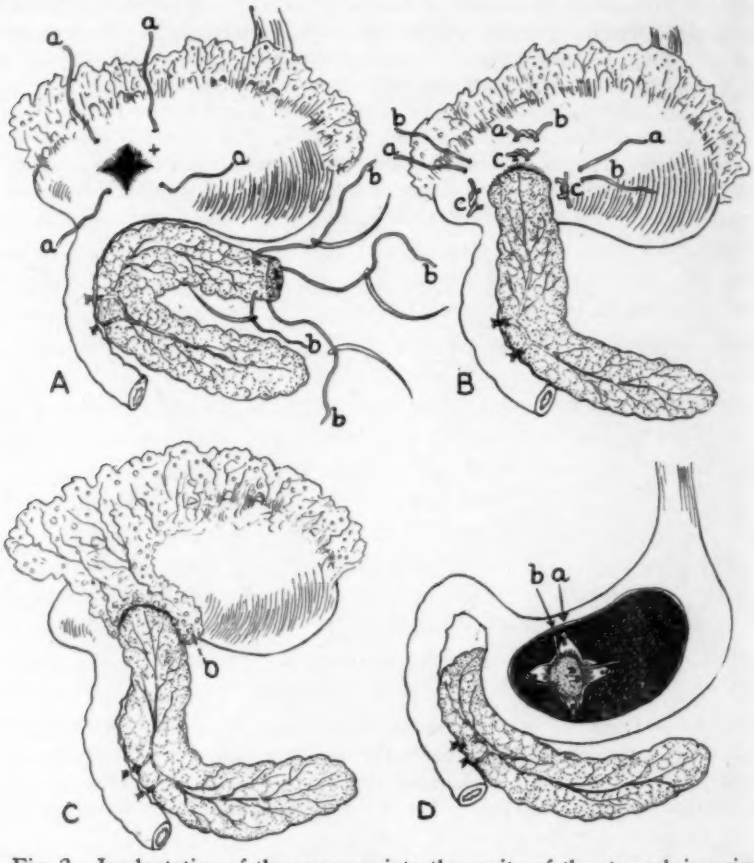

Fig. 2.—Implantation of the pancreas into the cavity of the stomach in series I: In *A*, *x* indicates the cross-incision in the posterior wall of the stomach; *a*, the flap-inverting sutures; *b*, the pancreas traction and anchoring sutures. In *B*, the pancreas is drawn into the stomach and its traction sutures (*b*) tied to the flap-inverting sutures (*a*); additional sutures of the stomach to the pancreas (*c*) are placed as in series II and III. In *C*, omentum (*o*) is sutured around the anastomosis as in series II and III. *D* shows the interior view of the anchored stump of the pancreas and the inverted stomach flaps, as in series II and III.

SERIES II

In this series we removed the head of the pancreas and implanted the remaining end into the cavity of the stomach (fig. 3). It must be stated here that in the dog the main pancreatic duct enters the duodenum from near the middle of the

pancreas. This duct was divided between two ligatures, but no attempt was made to sever all of the possible accessory ducts.

A study of the results of the operation again revealed good union between the wall of the stomach and the pancreas but no communication between the pancreas and the lumen of the stomach, probably for the same physiologic reason as in series I. The pancreas looked normal except for patchy foci of inflammation about the old sutures (figs. 7 and 8).

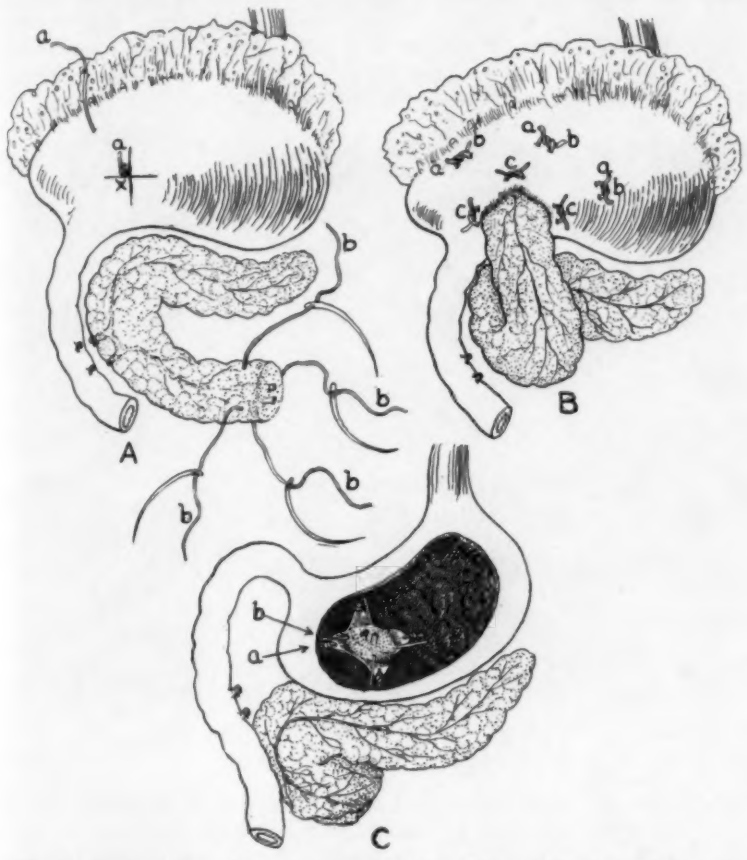

Fig. 3.—Implantation of the pancreas into the cavity of the stomach in series II. The explanation is the same as for figure 2, except that the head of the pancreas was removed and the stump was implanted into the cavity of the stomach.

SERIES III

In these experiments the head and neck of the pancreas were removed. The stump was dissected 1 inch (2.5 cm.) beyond the point where the pancreatic ducts enter the duodenum (fig. 4). Here an attempt was made to cut through all duct connections to the duodenum. The central duct was exposed from ½ to 1 inch and bleeding controlled. Clear pancreatic fluid could be plainly seen escaping

from the duct. The stump was then implanted into the posterior wall of the stomach as follows:

A triradiate or crucial incision, large enough to admit the end of the pancreas freely, was made into the posterior wall of the stomach about 1 inch above the great curvature and near to the pylorus, thus forming three or four flaps (fig. 4 *A*, *x*). A silk suture was passed through the point of each flap and tied. This was used to invert the flap by passing the suture into the cavity of the stomach and out through the wall 1 inch away from the cut edge. By pulling on

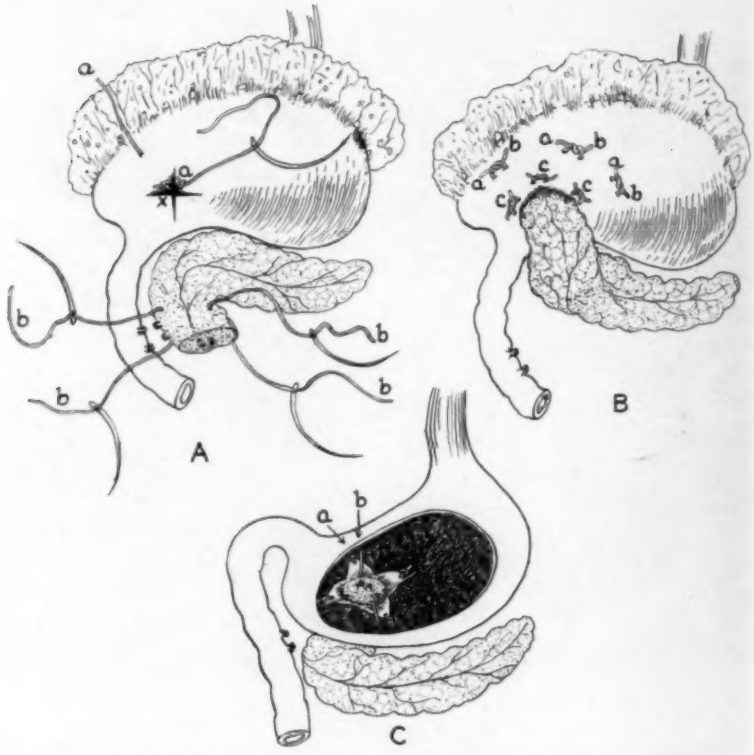

Fig. 4.—Implantation of the pancreas into the cavity of the stomach in series III. The explanation is the same as for figure 3, except that the head and neck portion of the pancreas was excised, and the stump with its duct orifices patent was implanted into the cavity of the stomach.

these sutures the ends of the flaps were inverted, a smooth peritoneal entrance for the stump of the pancreas being formed. One silk suture was passed through each side of the pancreas about 1 inch from the end to be implanted (fig. 4 *A*, *b*). These sutures were used as traction sutures to draw the stump of the pancreas into the lumen of the stomach. These were now carried through the aperture into the stomach and out again through the posterior wall a little distance from the exits of the flap-inverting sutures. These were then tied one to each of the flap-inverting sutures, thus anchoring the inverted ends of the flaps and preventing retraction of the pancreas (fig. 4 *B* and *C*, *a-b*). An additional row of sutures

was taken, the stomach being sewed to the pancreas (fig. 4 *B*, *c*). A small piece of omentum was drawn around the implanted pancreas and secured to the stomach wound by one or two sutures (fig. 2, *C*, *o*).

The abdomen was closed with catgut, without drainage, and the skin sutured with catgut and treated with iodine. Some of our dogs had been anesthetized with ethyl carbamate hypodermically. These died within forty-eight hours. In all we found serious hemorrhage into the stomach. We also lost several dogs from pneumonia. In no case was there any apparent leakage of gastric juice or any infection.

Of the surviving dogs, three were allowed to live for about nine months, during which time they were kept with a control dog. They fed on dog biscuits for about four months, then large amounts of meats and fats, then excess carbo-

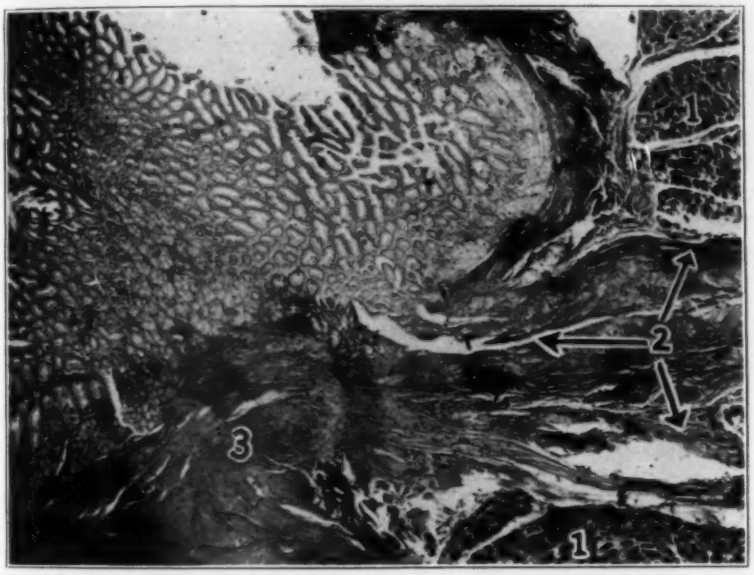

Fig. 5.—Photomicrograph showing normal pancreatic tissue (*1*), a pancreatic duct with its lumen (*2*) and the firm fibrous union to the muscularis of the wall of the stomach (*3*).

hydrates, and later on mixed refuse from the cafeteria. All the dogs lost weight on the dog biscuit diet but gained on a mixed diet.

Gastric contents, blood and urine were obtained at five week intervals.

Gastric analysis revealed that the pancreatic lipase (copper soap method) was strongly positive in all three dogs, except at one examination of one dog, and never in the control dog.

Trypsin was found in the stomachs of two dogs; questionable or negative reactions to the test were given by one dog, and trypsin was never found in the control dog.

Blood sugar varied from 50 to 105 mg. per hundred cubic centimeters in the dogs on which operation was performed, and from 66 to 83 mg. in the control dog. After four weeks on a diet high in carbohydrate, the blood sugar was 67, 71 and 71 mg. in the dogs on which operation was performed and 77 mg. in the control dog.

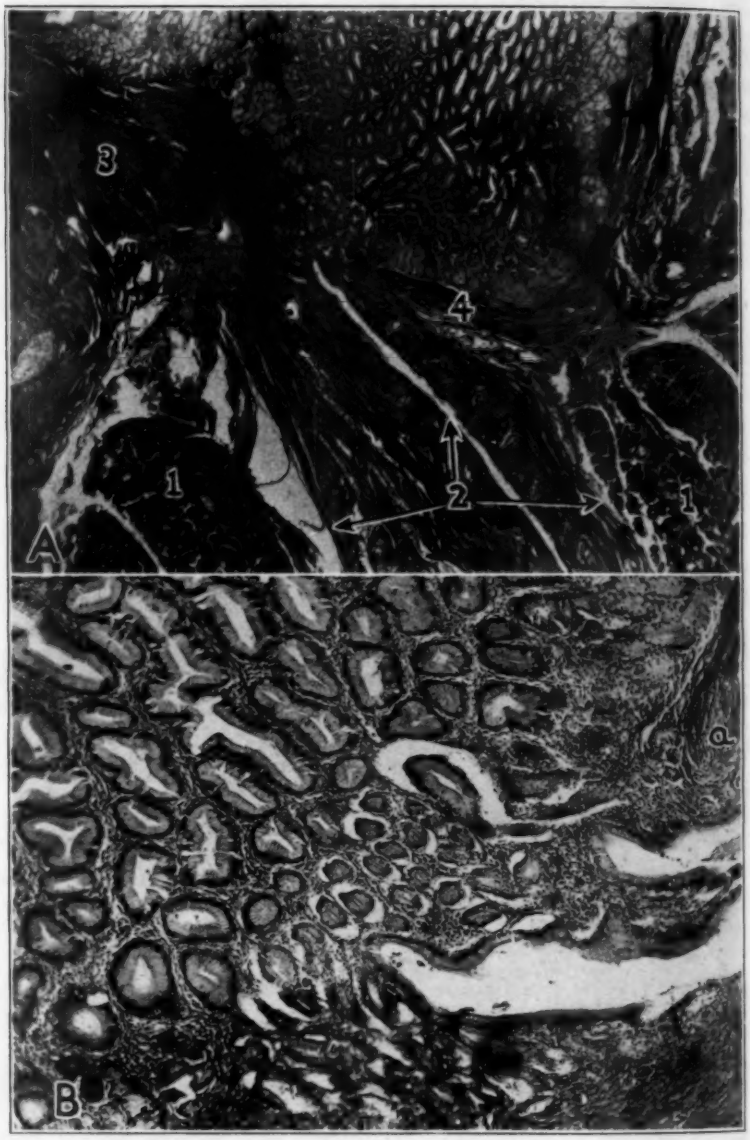

Fig. 6.—*A*, photomicrograph showing normal pancreatic tissue (*1*), a large pancreatic duct with its lumen (*2*), the firm fibrous union to the muscularis of the wall of the stomach (*3*) and muscularis mucosae (*4*). *B*, high power photomicrograph showing normal pylorus mucosae and glands, with continuity of the muscularis mucosae with the walls of the duct (*a*).

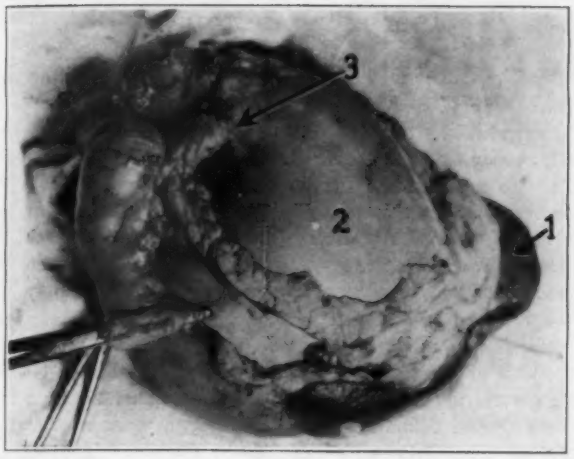

Fig. 7.—Fresh specimen from a dog six weeks after severance of the head of the pancreas and transplantation of the stump into the cavity of the stomach: *1*, spleen; *2*, posterior wall of the stomach; *3*, pancreas firmly united with the wall of the stomach.

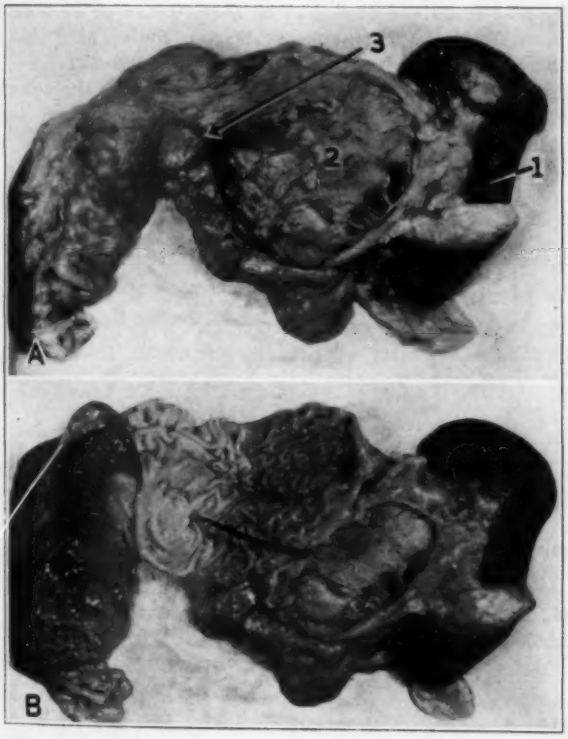

Fig. 8.—*A*, fresh specimen from a dog ten months after transplantation of the stump of the pancreas following excision of the head and neck: *1*, spleen; *2*, posterior wall of the stomach; *3*, pancreas healed to the wall of the stomach. *B*, inside view of the stomach showing the point where the pancreatic duct communicates with the cavity of the stomach.

Urine obtained by catheter never showed sugar in either the operated dogs or the control dog.

These dogs were killed after from nine to ten months. One dog which remained undernourished, at autopsy, after nine months, showed a gross complete atrophy of the pancreas, possibly due to the damage to its blood supply or to its ducts, but did have an enormous hypertrophy of the gastro-intestinal tract. This is undergoing further investigation. Microscopic examination of the site of implantation in the other dogs showed that the gross pancreatic tissue within the stomach was digested, but the duct was in continuity with the lumen of the stomach (fig. 5).

These two specimens in which the cephalic end of the pancreas was united to the stomach were cut in serial sections. In both specimens the pancreatic tissue attached to the wall of the stomach was normal, and a large duct was discovered just under the gastric mucosa (fig. 6). In one specimen the duct connection to the surface could not be definitely followed, although there were indications of a small duct system continuous with the gastric mucosa. The second specimen demonstrated a large pancreatic duct in which the lumen was continuous with that of the stomach, and continuity of the mucous membrane of the stomach with that of the duct was easily demonstrable (fig. 6). There was no evidence of any pathologic reaction within the wall of the stomach or the mucosa. The failure of the duct to heal in and establish continuity with the mucosa of the stomach in the first series, we attributed to the presence of an accessory duct or ducts, but it must be stated that in the first series the opening into the stomach was farther away from the pylorus than it was in the second series. The experimental evidence suggests that implantation should occur into the pyloric end rather than into the fundic end of the stomach. The free anastomosis about the pancreas seems to take care of the blood supply of pancreatic tissue no matter which part is implanted, and this is borne out by the excellent preservation of the pancreatic substance, both in gross and in microscopic specimens (figs. 5, 6, 7 and 8).

CONCLUSION

The pancreas may be successfully implanted in the stomach, and its internal and external functions preserved.

The establishment of the possibility of surgical connection between the pancreas and the stomach opens an extensive program of research for both surgical and physiologic investigators.

Drs. H. N. Allen and O. E. Hagebush performed the biochemical examinations; Drs. William Collier and A. G. Pohlman, the microscopic examinations, and our chief, Dr. W. T. Coughlin, at whose request and suggestion we undertook this work, gave valuable aid.

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CRANIAL OSTEOMAS AND HYPEROSTOSES PRODUCED BY MENINGEAL FIBROBLASTOMAS

A CLINICAL PATHOLOGIC STUDY

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NEW YORK

Clinically, an osteoma of the cranial surface may sometimes closely simulate a hyperostosis produced by a meningeal fibroblastoma (dural endothelioma, meningioma). The importance of distinguishing between these two lesions, so different in their ultimate results, lends intrigue to an already interesting study.

In the recent literature considerable attention has been given to hyperostoses resulting from infiltration of the skull by meningeal fibroblastomas. From a clinical and operative point of view, this attention has also been extended to osteomas about the frontal sinus [1] and orbit.[1a] A study of osteomas of the external surface of the cranium, however, would appear to have been largely neglected. Judging from the material in this laboratory, the latter osteomas occur almost as frequently as clinically recognizable hyperostoses cranii produced by meningeal tumors.

An attempt shall be made in this paper to explain the true nature of osteomas of the external surface of the cranium as well as their clinical, pathologic and roentgenographic differentiation from hyperostoses produced by meningeal fibroblastomas.

The material for this article was collected in the Surgical Pathological Laboratory of the Johns Hopkins Hospital from approximately 2,000 cases of tumors of the bone and 1,000 cases listed under tumors of the head and skull, which included approximately 350 cases of tumor of the brain. All the osteomas of the external surface of the cranium or hyperostoses caused by meningeal fibroblastomas were verified by microscopic examination.

OSTEOMAS OF THE EXTERNAL SURFACE OF THE CRANIUM

Under this heading are included osteomas which apparently arise from preosseous tissue on the cranial surface. If one attributes osteo-

From the Department of Surgery and Surgical Pathology, Johns Hopkins Hospital and University, Baltimore.

1. Armitage, George: Osteoma of the Frontal Sinus with Particular Reference to Intracranial Complications, Brit. J. Surg. **18**:565, 1931.

1a. Cushing, Harvey: Experiences with Orbito-Ethmoidal Osteomata Having Intracranial Complications, Surg., Gynec. & Obst. **44**:721, 1927.

genic powers to the periosteum, then these osteomas may be regarded as apparently arising in the deeper layers of this tissue. On the other hand, if one is of the belief that the periosteum includes only the outer layer of fibrous tissue covering the skull, which seems to act as a limiting membrane only, then these osteomas must be regarded as apparently originating in the underlying preosseous tissue.

Whether the cranial osteomas should be classed as true neoplasms is a debatable question. Ewing [1b] wrote:

> Circumscribed overgrowth of bone occurs under such a wide variety of conditions and the distinction between inflammatory and neoplastic hyperplasia of the tissue is so often obscure that it has never been possible to define the limits of osteomata. In discussions of osteomata, it is customary to include all forms of overgrowth of bone, thus securing an effective comparison of true and partial bony neoplasms.

Not quite such a broad classification is adhered to in this article, as there are a number of osteomas arising from the external surface of the cranium, which appear to comprise a distinct group with special characteristics, that are worthy of individual consideration. In order to define the boundaries of this special group, it is well to exclude those apparently similar cranial osteomas arising from the frontal sinuses, orbit and inner table of the skull, the ventral symmetrical hyperostoses of the inner table of the calvarium and also certain other lesions with known etiology, often referred to as osteomas, such as hyperostoses produced by osteomyelitis, syphilis and similar conditions, and finally, osteochondromas. The groups not included in the main class of cranial osteomas to be presented deserve brief mention.

Osteomas of the frontal sinus and orbit are not well represented by the material from this laboratory. Their origin and mode of development are still the subject of debate. Many of them appear to arise from the deeper layers of the periosteum or subperiosteal preosseous tissue and present in their growth both spongy and eburnated forms. They apparently are the result of a process similar to that special group of osteomas to be described. They arise in a different situation and, unlike osteomas of the cranial surface, cause early damage to vital structures. They sometimes cause a swelling of the outer table of the skull by pressure, but by roentgenographic study are easily distinguishable from osteomas arising on the cranial surface.

Osteomas of the inner table, which have also been excluded from detailed description, seem to represent a similar process, but appear to arise from the endocranium on the intracranial surface of the skull. Three osteomas of this type were found in the laboratory. None of them showed a demonstrable change in the outer table of the skull.

1b. Ewing, James: A Text Book of Neoplastic Disease, Philadelphia, W. B. Saunders Company, 1928.

In their symptomatology they were indistinguishable from meningeal fibroblastomas.

Symmetrical hyperostoses of the inner table of the calvarium usually are found only at autopsy, occur most frequently in females and are confined particularly to the frontal region. They are usually symptomless. Yolton's [2] paper should be consulted for a more detailed description.

The other cases found in the laboratory which should be excluded before a presentation of the more special group of osteomas is attempted are as follows: One was the case of a man, aged 34, who presented exostoses of the frontal, malar and clavicular bones and a positive Wassermann reaction; the growths disappeared rapidly following antisyphilitic treatment. In the next case there was a microscopically unverified osteoma of the external auditory canal, apparently similar to that reported by Lillie and Williams.[3] The last case was that of a patient, aged 15, presenting an osteochondroma of the occipital bone at the site of attachment of the trapezius muscle (fig. 1). The fact that in the roentgenogram this tumor showed a cartilaginous cap and arose from the basi-occipital bone, which is preformed in cartilage, at the site of attachment of the trapezius muscle in the tendon of which precartilaginous connective tissue may be found, excludes this case from the main series to be described.

When the foregoing cases are excluded, there is left a group that presents special characteristics. This group is the one presented here.

The special group of osteomas discussed in this paper are benign bony tumors usually arising before or about puberty from the external surface of the cranium and most frequently involving the frontal bone. The symptoms, as a rule, are mild, but rarely definite signs of compression of the brain or of cortical irritation may arise late in the course of the disease. In this series the average duration of the tumor at the time of operation was nineteen years, but a case is recorded with a history of only one year's duration and another of sixty-six years. The roentgenographic picture varies according to the stage of development of the tumor. Thus, it may show a small button-like tumor on the surface of the outer table, an enormous subperiosteal bony tumor with complete absorption of the outer table and involvement of the diploe in places, or, finally, a spongy or eburnated osteoma lying with its base on the inner table and showing on its surface a bony shell. Microscopically, the tumors are either eburnated and composed of quiescent adult corti-

2. Yolton, L. W.: Ventral Symmetric Hyperostosis of Inner Table of Calvarium, Tr. Chicago Path. Soc. **13**:181 (June) 1930; Arch. Path. **9**:534 (Feb.) 1930.

3. Lillie, H. I., and Williams, H. L.: S. Clin. North America **11**:801 (Aug.) 1931.

cal and cancellous bone, or spongy with proliferating preosseous tissue and young trabeculae of cancellous bone. Between these two types are found osteomas showing intermediary stages of ossification. On the surface of apparently all types of osteomas is a layer of fibrous tissue (periosteum), which in the spongy type and in certain small areas in the eburnated type shows in its deeper layers a gradual transition through a fibrospindle cell stage to an adult preosseous tissue, actively concerned in bone formation. Later it is pointed out that the eburnated and spongy osteomas are only different stages of the same process, and that they apparently all arise from the deeper layers of the periosteum or subperiosteal preosseous tissue which lies on their surface.

Fig. 1 (path. no. 47270).—Roentgenogram showing an osteochondroma arising from the occipital bone near the attachment of the trapezius muscle, the tendon of which contains precartilaginous connective tissue. Note the cartilaginous cap and the tendency of the tumor to develop in a longitudinal manner, outwardly from the bone.

PRESENTATION OF CASE HISTORIES

CLINICAL FEATURES

The present analysis is compiled from nineteen cases of osteoma of the outer surface of the cranium reported in the literature and seven cases found in the Surgical Pathological Laboratory of the Johns Hopkins Hospital.

All of the patients complained of a bony hard tumor or osteoma of long duration attached to the surface of the skull.

Etiology.—In five cases, the sex was not recorded, but in the others, twelve of the patients were females and nine males. There was a history of trauma prior to the appearance of the tumor in eight cases, but the majority seem to have arisen spontaneously. A low grade periostitis may have played a rôle in the production of some of the growths and particularly in those in which the skin was broken at the site of trauma and in those arising near the frontal sinuses or mastoid portion of the temporal bone, but there is no definite proof of this. No history of rickets was noted in this series.

In no case was there any suggestion of a hereditary factor influencing the growth of the osteoma, although in two cases the tumor was present at birth. Trauma at birth must be considered as a possible factor.

It is interesting to note that in fifteen cases the patient was 12 years of age or younger when the growth first appeared, and in ten cases the osteoma was noted before the patient was 8 years old. No age of onset is given in five cases, but the eldest of these patients was 31 years old and when one considers the slow growth of the usual osteoma, it is logical to believe that these five patients also were young at the onset of the tumor. The other six patients ranged from 14 to 31 years of age when the tumor appeared.

Signs and Symptoms.—A bony, hard, nonmovable, painless lump protruding from the surface of the skull was the first sign noticed in all patients.

In the twenty-six cases, thirteen osteomas were almost totally restricted to the frontal bone. Five tumors involved particularly the parietal bones, but three of these also involved the frontal bone. The remaining eight tumors were attached to the temporal bone, but several of these encroached on the parietal bone and two on the occipital.

The majority of the osteomas grew slowly and steadily, but in some cases trauma to the tumor or incomplete removal at operation precipitated an acceleration in growth. In case 23, the tumor appeared spontaneously to grow more rapidly about puberty.

The great majority of histories indicate that the condition was symptomless, but in the histories of more recent years and particularly in my own cases, dizziness, headaches, a sense of pressure and pain about the lump were noted. From only three patients was there obtained a history of symptoms of cerebral damage, one of these having had epileptic seizures fifty-three years after the onset of the tumor, another increasing symptoms of a right-sided cerebral lesion following a serious fracture of the skull in infancy, and the third patient (case 5), mental retardation. Fainting spells were noted in case 7, but these may have been functional.

The duration of the tumor at the time of operation is recorded in nineteen cases, and in fourteen of these there was a history of over eleven years, the average time being twenty-four years. The histories in the other five cases dated back from one to ten years. The average duration of the tumor, taking the nineteen cases collectively, was nineteen years.

The rarity of severe symptoms and the protracted course of these lesions indicated their benignancy. Von Eiselberg [4] and Bassoe [5] each reported a case with secondary malignant change in an atypical cranial osteoma. Bassoe's case was that of the famous giant, Wilkins. Secondary sarcomatous change in exostoses (osteochondromas) elsewhere in the body is comparatively common, but these tumors, as is well known, are chondromyxosarcomas, having their origin in precartilaginous connective tissue which is apparently absent about the cranial vault. Geschickter [6] collected eighty of these cases.

Physical Examination.—As far as can be ascertained, the majority of the patients appeared healthy and intelligent, but there was some mental retardation in case 5. In only one instance (case 5) is there a record of fever or increase in the pulse rate, and in this case the cause of the fever was uncertain.

The osteomas varied in size from that of a small walnut to that of a grape-fruit, but the original tumor in some cases was as small as a pinhead. The skin over the growth was freely movable and appeared normal except in case 7, in which an increase in vascularity was noted, and in a few cases in which a scar of a previous operation was present. The majority of the osteomas were in the frontal region and four of them at least involved the glabella of this bone. In every case the tumor was bony, hard, nonmovable and firmly attached to the skull. In most cases, it was smooth, rounded, broad-based and semispherical, and appeared to shade imperceptibly into the surrounding skull. In some cases, the surface was slightly irregular and somewhat lobulated. Small button-like osteomas lying on the external table of the skull have been mentioned by Virchow,[7] and a picture of a similar osteoma on the surface of the frontal bone is shown by MacCallum [8] "separated from

4. von Eiselberg, F.: Zur Casuistik der Knocheren Tumoren des Schadeldaches, Arch. f. klin. Chir. **81**:1, 1906.

5. Bassoe, P.: Concerning an Exostosis of the Skull Undergoing Sarcomatous Change, J. Nerv. & Ment. Dis. **30**:513, 1903.

6. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, New York, American Journal of Cancer, 1931.

7. Virchow, R.: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1863, vol. 2, p. 1.

8. MacCallum, W. G.: A Text Book of Pathology, Philadelphia, W. B. Saunders Company, 1928.

the skull around the edges so as to appear pedunculated." Similar small osteomas have been found attached to the surface of the facial bones.

Two osteomas were present on the skull in four of the cases, and tenderness over the growth was present in two. Osteomas were found elsewhere on the skeleton in two cases, and there was also a case in which there were symptoms of a right-sided cerebral lesion with signs of left hemiplegia, internal strabismus and a history of fractured skull. Percussion over the osteomas gave results similar to that done elsewhere over the cranium, and no cracked-pot sound was noted. Auscultation when done likewise gave negative results.

General physical and neurologic examinations gave apparently negative results, except as already stated. The white blood cell count was slightly elevated in two cases. This may have been due to poor counting, as the hemoglobin, temperature and pulse rate were normal in these cases. No other abnormalities in morphologic or serologic blood studies were recorded, nor was there anything of importance noted in the urine of these patients.

ROENTGENOGRAPHIC FEATURES

The literature unfortunately contains little of value concerning the roentgenographic features of the osteomas of the cranial surface. Only seven good roentgenograms were found, two of these in the literature (cases of Marey [9] and Orator [10]) and five in this laboratory. All the tumors, six of which were of the spongy type and one of the eburnated type, had been present for over twelve years when the roentgenograms were taken.

Although the number of roentgenograms available limit the scope of the study, there are many features characteristic of osteomas which give valuable clues to their origin, mode of growth and early appearance, as well as aid in differentiating them from other cranial lesions.

The seven roentgenograms show a smooth or slightly irregular and in some cases faintly lobular domelike swelling, extending outward for a varying distance from the surface of the skull. The base of the mound in every case is formed by the inner table of the skull which appears thickened and in most cases slightly depressed.

In six cases the body of the tumor is continuous with the diploe, the outer table of the skull having completely disappeared. In the rotengenograms for cases 1, 4, 5 and 6, a thin layer of bone extends over the surface of the dome of the tumor, being most pronounced in

9. Marey, Georges: Contribution à l'étude d'une variété particulière d'exostose de la voûte crânienne, le spongiostéome, Thèse de Paris, 1910, no. 87.

10. Orator, V.: Beitrag zur Chirurgie der Schadeldachosteome, Deutsches Ztschr. f. Chir. **233**:459, 1931.

case 1 in which the growth is an eburnated osteoma. These roentgenograms give one the impression that the tumor arose in the diploe and pushed the outer table before it in its growth. This is what appears to have taken place and is the accepted theory, but it seems unlikely that a new growth arising in the diploe could produce an original tumor the size of a pea, which was true in case 5 (fig. 2), without first passing through the outer table. If the growth did pass through the outer table, then the theory of its expansion before the tumor is incorrect. If the tumor arose in the diploe, the swelling would in all probability have been more fusiform with more depression of the inner table than is seen. Microscopically, it is shown below that the shell of bone over the surface of these neoplasms is new bone in the process of being formed from preosseous tissue and is not the expanded outer table.

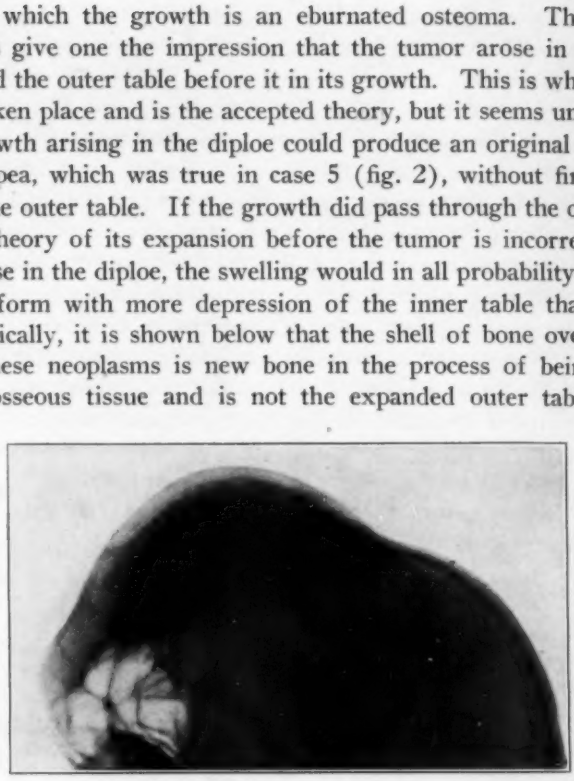

Fig. 2 (case 5).—Roentgenogram of an enormous spongy osteoma which arose from preosseous tissue on the surface of the frontal bone. The tumor is continuous with the diploe. A thin shell of new bone lies on its surface, and its base is formed by a thickened and slightly depressed inner table of the skull. The inner table, although wavy in outline, is smooth and clearly demarcated. The frontal sinuses are enormous, but there is no tendency for the tumor to fill them.

The density of the body of the osteomas varies from about that of the diploe to a very dense shadow, as is seen in the eburnated tumor. The dome of the tumor in Orator's [10] case presented an irregular mottled appearance of increased density, characteristic of the irregular laying down of more adult bone. An anteroposterior view of some spongy osteomas shows what appears to be an erosion of the skull. The spongy nature of the bone is usually responsible for this appearance of erosion.

The frontal sinuses are enlarged, although empty, in those cases in which the tumor encroaches on the glabella of the frontal bone. In one case they are enormous (fig. 2).

The roentgenogram (fig. 4) in case 7 presents a picture of considerable importance, as it gives some indication of the origin and subsequent

mode of growth of these tumors. It shows particularly the lateral edge of the tumor where there is evidence of a largely absorbed, moth-eaten looking, but still partially persistent, outer table of the skull, passing through the depth of the tumor with the greater portion of the tumor overlying this outer table. At the extreme periphery of the osteoma where the outer table is best preserved, there is considerable bony subperiosteal proliferation. The diploic space throughout appears little wider than normal. A roentgenogram of a cross-section taken through the center of the tumor, however, shows no evidence of the old outer table; it apparently had undergone complete spongy transformation or absorption (fig. 5). Roentgenographically, the tumor as a whole presents a fluffy mottled appearance with areas of increased porosity and new bone formation with a tendency for the bone spicules to be laid down in a somewhat peripherally radiating fashion on its surface.

Fig. 3 (case 6).—Roentgenogram showing a spongy osteoma involving the frontal bone. The tumor shows a very thin shell of new bone on its surface. It is continuous with the diploe. Its base is formed by a thickened and slightly depressed inner table of the cranium. The inner surface of the skull underlying the osteoma is smooth. The left frontal sinus is enlarged. This tumor was eburnated at its lower periphery.

This picture in a long bone would suggest a malignant growth. This malignant appearance is frequently seen in benign growths arising in membranous bone. The base of the tumor in its middle portion, as pointed out, is formed by a somewhat thickened and slightly depressed inner table.

From figure 5 it appears that the osteoma did not arise in the diploe, but in the periosteal region where the formation of considerable new bone of a porous appearance occurred, and finally most of the outer table became absorbed or likewise transformed into spongy bone. This spongy transformation of the outer table is seen particularly in the cross-section through the center of the tumor. The tumor, therefore, in time having completely absorbed the outer table of the skull, would be everywhere continuous with the diploic space and appear to be arising

from it. If these observations are correct, this osteoma represents an earlier stage in development than the six osteomas previously described, in which the old outer table had completely disappeared in the regions of the osteoma, and in some cases a layer of bone had been laid down on the surface of the tumor. Carrying the idea further, one may imagine

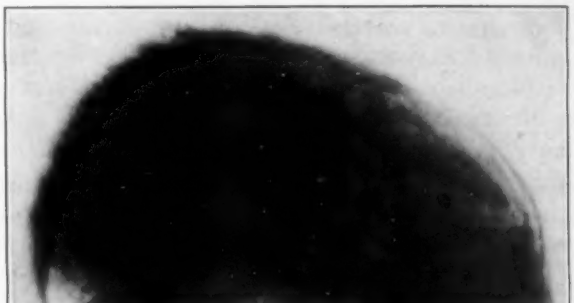

Fig. 4 (case 7).—Roentgenogram showing the periphery of a spongy osteoma. Subperiosteal bony proliferation overlying a partially intact outer table of the skull is evident, especially at the right hand edge of the osteoma. The plate shows evidence of some radial arrangement of the new bone. This picture could be easily confused with one of an exostosis overlying a meningeal fibroblastoma. Figure 5, taken to show the central regions of the tumor, easily differentiates it from a hyperostosis of meningeal origin. Note that the inner table is slightly depressed, but clearly outlined.

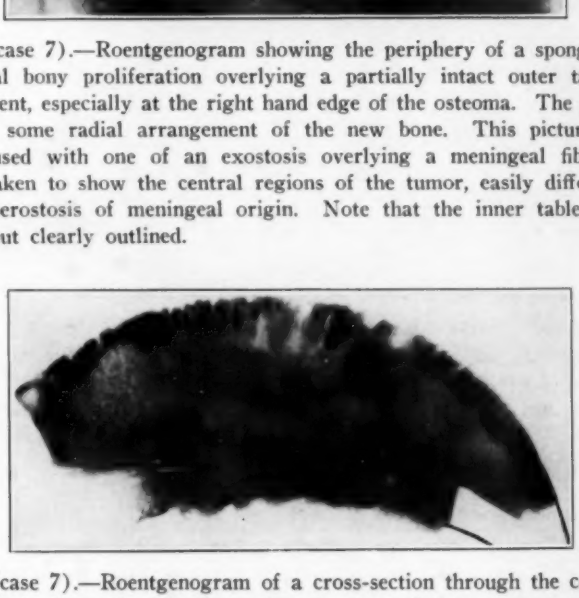

Fig. 5 (case 7).—Roentgenogram of a cross-section through the center of the tumor shown in figure 4. The dome-shaped nature of the spongy osteoma is well shown here. The outer table of the skull has undergone a spongy transformation or absorption and is no longer evident. The bone is arranged in a radiating fashion only near the surface of the tumor. The inner table shows the markings of the meningeal vessels, and, unlike the exostoses produced by meningeal tumors, shows no evidence of new bone formation extending downward from its inner surface. The roentgenogram was taken at an angle which accounts for the appearance of roughening on the inner surface of the skull.

that the osteoma in case 7 was originally a small spongy growth arising on the surface of the outer table. In support of this idea, it should be

mentioned that I have found a number of small, spongy osteomas in the periosteal region about the membranous bone of the face.

GROSS PATHOLOGY

A correlation of the observations recorded at operation with those made on examination of the gross specimens proves of value in the determination of the nature of these cranial osteomas. Although many of these tumors present a difference in gross structure, the origin and mode of growth appear to be essentially the same in all types. These differences in gross structure seem to represent only separate stages in the development of osteomas. The nature of the tumor appears to be influenced in part by the age of the patient.

In the gross some of the tumors lie flat on the surface of the skull, apparently being attached only to the outer table. Others appear to penetrate as far as the outer layers of the diploe, and there are finally tumors which lie with their base on a thickened and slightly depressed inner table, the outer table having completely disappeared.

The consistence of these osteomas likewise varies, some being spongy and cancellous (spongy osteomas), others eburnated or hard (eburnated osteomas).

Even among the spongy type differences in structure can be detected, but apparently all of them show dense fibrous tissue on their surface, which fuses with the surrounding periosteum. This fibrous tissue is often abundant. Some of the tumors show a layer of bone beneath this fibrous tissue, while in others it is absent. This layer of bone may be continuous, thick and hard, or irregularly distributed, thin and easily broken through. When it is present, it is usually continuous with the outer table of the skull, and beneath it there is relatively avascular, tough, cancellous bone continuous with the diploe. In those cases in which no layer of bone is present, the fibrous tissue on the surface becomes directly continuous with an underlying soft, vascular, more mushy cancellous bone than that above, which usually can be followed inwardly to the inner table of the skull and is everywhere in direct continuation with the diploe. The larger osteomas arise, as a rule, before puberty and are usually of the spongy type that show cancellous bone extending to the inner table.

The so-called eburnated osteomas present a more uniform picture. The same type of fibrous tissue lies on their surface, but cortical bone is present beneath this tissue in all cases. Extending toward the depth of the tumor from the undersurface of the cortical bone, there is usually adult cancellous bone which is hard and much more difficult to cut than that encountered in the spongy osteomas. Cortical bone may, however, predominate throughout the whole tumor. The eburnated tumors are, as a rule, small and may lie with their base on the inner table or, per-

haps, as in the cases mentioned by Virchow [7] and MacCallum,[8] may lie flat on the surface of the skull like a button, being attached only in their more central regions. This type of tumor is more common about the facial bones. Of the five patients in this series who were over 21 years of age at the onset of the tumor, four presented osteomas of the eburnated type, and in case 1, although the nature of the original tumor is not known, the recurrent one arising when the patient was 22 years of age was of the eburnated type. A tendency of the osteomas arising in adults to be eburnated is therefore evident.

It should be mentioned that in case 3 two small perforations of the skull were present at the edge of the osteoma. Infection may have been a factor in this case.

MICROSCOPIC FEATURES

The microscopic picture of an osteoma of the outer table of the cranium varies according to the stage of development of the tumor and the age of the patient. On the surface of apparently all of the osteomas, there is a layer of fibrous tissue (periosteum) under which may or may not be a layer of cortical bone. The center of the tumor is usually made up of cancellous bone, either of the young or of the adult type.

The microscopic picture of an eburnated osteoma shows on the surface of the tumor a comparatively thick layer of hyalinized looking, relatively anuclear fibrous tissue (fig. 6), which in some sections shows small areas of underlying preosseous tissue which is engaged in the formation of new bone (fig. 7). This fibrous tissue is firmly adherent to underlying cortical bone and in many places dips into it, forming a homogeneous union with the bone. The underlying cortical bone is of the adult type with well defined, concentrically arranged lamellae and small haversian canals, and is relatively avascular. This bone usually shows a gradual transformation to a more cancellous type as the center of the tumor is approached, and in this region is seen an interlacing of adult laminated bony spicules, with relatively wide intertrabecular spaces containing scanty but normal looking hematopoietic elements. In some of the osteomas, cortical bone predomintes throughout (fig. 6). These eburnated osteomas may present a layer of cortical bone on their inner as well as on their outer surface, which is the old, inner table of the skull (fig. 8). In some of these tumors no formation of new bone is seen except subperiosteally (fig. 7).

The microscopic sections of the spongy osteomas do not show such a quiescent picture. On the surface of the tumor is seen a hyalinized-like fibrous tissue, poor in nuclear material and identical in appearance to that described previously (periosteum). But in the deeper layers of this connective tissue, there is a gradual transition from an elongated spindle cell stage to a more mature definite preosseous tis-

sue containing young osteoblasts (figs. 9 and 10). The osteoblasts are lined in rows along irregularly scattered trabeculae of young bone in the formation of which they are actively participating. Over a small area toward the surface of the tumor in some sections, there is a tendency for the new bone to be laid down in a peripherally radiating fashion (fig. 9), but elsewhere throughout the tumor the trabeculae are everywhere arranged in an irregular manner. This irregular distribution of trabeculae is well shown in the roentgenogram. In some of the sections of this type, the spongy bone extends from the surface of the

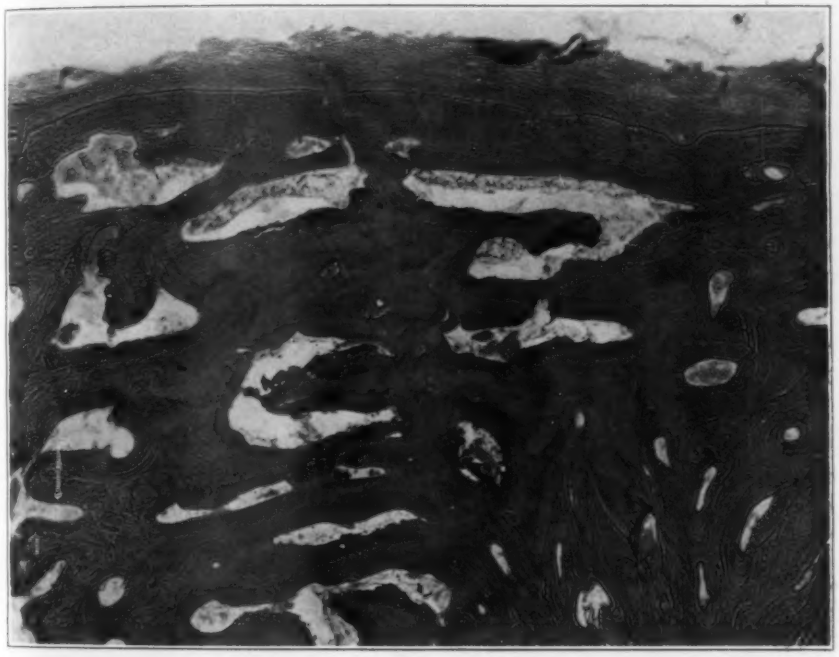

Fig. 6 (case 1).—A low power photomicrograph of an eburnated osteoma showing abundant quiescent, relatively anuclear fibrous tissue (periosteum) on its surface.

tumor to the inner table of the skull, the inner layers of which are sometimes transformed into spongy bone of a more dense nature than that seen in the center of the tumor (fig. 11). This type of spongy bone extends over a wider area than the normal inner table and hence could account for the thickening seen in the roentgenograms. In no section is there evidence of new bone formation on the part of the endocranium (endosteum), and if this does take place in some cases, it must be small in amount or severe symptoms of compression of the brain would ensue, which rarely happens in this type of osteoma.

On the contrary, the endocranium appears to act in some measure as an internal limiting membrane preventing any marked depression of the inner table. It is possible in some cases that the inner table may become completely transformed into spongy bone, and although this has never been observed, it would account for the slight depression of the inner table which is so frequently seen. In some osteomas of the spongy type, a layer of bone lies under the periosteum (fig. 12). Beneath this layer, although young cancellous bone is present, it appears less vascular and more mature than in the type lacking a layer of surface bone. It is important to note that the layer of surface bone at first is young in type and is actively being formed from preosseous tissue. It cannot, therefore, be the expanded outer table. There are osteomas which show intermediary stages of ossification between all the aforementioned types. It would seem, therefore, that they represent only different stages in the development of a similar process.

Fig. 7 (case 6).—Low power photomicrograph of the eburnated edge of a spongy osteoma. Small quantities of new bone are being laid down subperiosteally on the surface of cortical bone in the upper left hand portion of the picture. A few osteoblasts can be seen on the surface of the bone. Note the relatively anuclear appearance of the fibrous tissue in the extreme upper left hand corner.

It should be mentioned that giant cell osteoclasts are seen scattered irregularly throughout the preosseous tissue in the spongy osteomas. In some places they are in apposition with bony spicules where they lie in little "lacunae."

As the result of trauma or some other less clearly understood stimulus, eburnated osteomas, which as a rule are small, in youthful patients appear able to take on a more active growth and hence are converted into a spongy form, which type comprises the majority of the

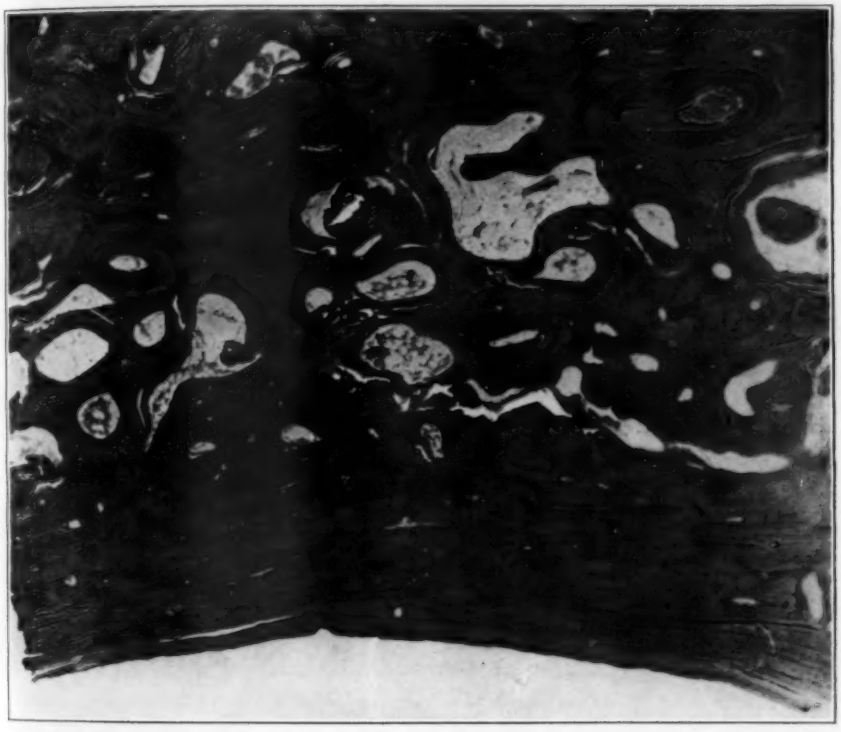

Fig. 8 (case 1).—A low power photomicrograph of an eburnated osteoma showing the smooth inner surface of the skull from which the endocranium has been stripped.

larger tumors. In 1863, Virchow [7] recorded a similar observation. He recognized that certain cranial osteomas, originally of a porous nature, became eburnated in their later growth and were finally reconverted into a spongy form. These observations have been largely neglected by more recent authors.

In the central regions of a spongy osteoma the microscopic picture is similar to that seen in most benign ossifying lesions, such as Paget's disease, ossifying periostitis and osteitis fibrosa or in the wall of a bone cyst.

HISTOGENESIS

In the foregoing analysis, much evidence was presented clinically, roentgenologically, grossly and microscopically that certain osteomas arise from preosseous tissue on the cranial surface and that these osteomas when actively growing are spongy and usually absorb the outer table of the skull, but when slowly growing or when the end-stages of ossification have been reached, they are eburnated and usually relatively quiescent. A review of the embryology and subsequent

Fig. 9 (case 7).—Low power photomicrograph showing the surface of a spongy osteoma. Hyalinized relatively anuclear fibrous tissue (periosteum) on the surface gives place in its deeper layers to adult preosseous tissue engaged in bone formation. The tendency for the spicules of new bone to be laid down in a peripherally radiating fashion is seen here at the surface of the tumor, but in its deeper layers they are laid down in an irregular fashion.

growth of the normal skull as well as the histogenesis of bone in general supports these observations.

It is generally accepted that the bones of the cranial vault and face (including the interparietal, parietal, frontal, squamous and tympanic bones, the median pterygoid plate of the sphenoid, the nasal, lacrimal and malar bones, the palatine, vomer, maxilla and a portion of the mandible) undergo intramembraneous ossification, being formed

directly from the mesenchymal blastoma without the intervention of cartilage, and that the other bones of the skull are preformed in cartilage and undergo endochondral ossification. From this it is evident that embryologically as well as histologically, as was shown in the microscopic sections, the osteomas of the cranial vault, which type comprised the great majority of this series, originate directly in preosseous tissue and not in cartilage, or precartilaginous connective tissue which is absent in this region. Although Cohnheim's theory of cartilaginous "rests" could possibly be advanced in connection with

Fig. 10 (case 7).—Photomicrograph showing a higher magnification of the surface of the spongy osteoma seen in figure 9. In the upper right hand corner is seen relatively anuclear hyalinized fibrous tissue (periosteum). This hyalinized fibrous tissue in its deeper layers shows a transition through a fibrospindle cell stage to preosseous tissue containing osteoblasts which in places are lined in rows along young trabeculae of new bone in the formation of which they are actively participating. Probable evidence that osteoclasis goes hand in hand with osteogenesis is supplied by the presence of a few giant cell osteoclasts applied to the new-formed body spicules.

osteomas having their origin in bones preformed in cartilage, it does not seem logical to apply it to those of the vault of the skull, nor, in fact, even to those of the temporal bone where no cartilage has been seen microscopically.

The fact that the normal membranous bones of the skull increase in thickness by a deposition of bone subperiosteally and in the outer table around the walls of the vascular channels directly from preosseous tissue with no intervening cartilaginous stage, accompanied by an internal reconstruction or absorption of old bony lamellae within, lends weight to this argument and presents a plausible site of origin for the osteomas, a site to which all evidence so far given in this paper has pointed.

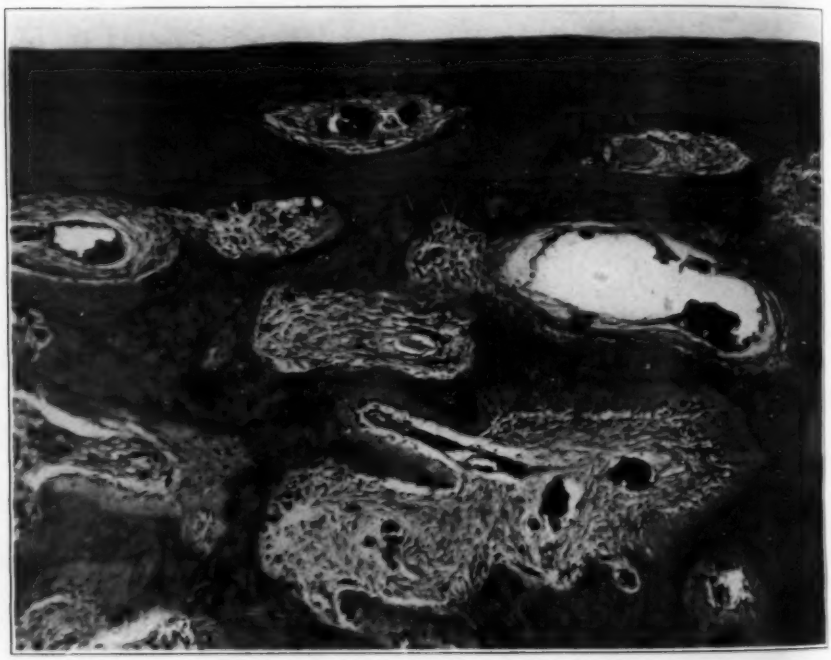

Fig. 11 (case 7).—Relatively high magnification of the inner table of the skull involved in a spongy osteoma. Note its partial spongy transformation, its smooth quiescent inner surface and the absence of endocranium (endosteum).

For almost two centuries a controversy has been in progress concerning the osteogenic function of the periosteum. In 1739, Duhamel,[11] in speaking of long bones, asserted that new bone was formed by the periosteum assisted by the endosteum. Since then he has had many followers, including Symes,[12] Flourens,[13] Ollier,[14]

11. Duhamel, quoted from Haas.[16]

12. Symes, quoted from Haas.[16]

13. Flourens, Marie-Jean Pierre: Recherches sur le développement des os et des dents, Paris, Gide, 1842.

14. Ollier, Louis: Traité expérimental et clinique de la régénération des os et de la production artificielle du tissu osseux, Paris, V. Masson & fils, 1867.

Axhausen [15] and Haas.[16] Opposed to this theory of the osteogenic rôle of the periosteum there have been among others Haller,[17] Hunter,[18] Goodsir,[19] MacEwan [20] and Stump.[21] Additional complications are supplied by MacEwan,[20] who expressed the belief that the growth in diameter of the shaft of a bone is a result of interstitial growth of the bone itself. Stump,[21] in 1924, presented evidence that the periosteum is an end-differentiation of primitive connective tissue (mesenchyme) and that it serves only as a "limiting membrane," the growth in thickness of a bone resulting from subperiosteal osteoblasts and undifferentiated connective tissue cells (mesenchymal remnants) which are intimately blended with the deeper layers of the periosteum. MacEwan [20] previously formulated the theory that the periosteum functioned as a "limiting membrane" only.

Thus, if one can apply the foregoing theories to the development of the cranial osteomas, they may be regarded as arising either in the deeper layers of the periosteum or else subperiosteally, depending on one's definition of the word periosteum. It does not seem likely that they arise from interstitial growth in the surface of the outer table, but this cannot be disproved here. Microscopically, the hyalinized-like fibrous tissue on the surface of the osteomas appears in some cases (figs. 9 and 10) to give rise to elongated spindle cells, which in turn seem to develop into adult osteoblasts. From Stump's observations, however, it would seem rather that the hyalinized fibrous tissue was an end-product of the preosseous tissue underlying it.

The function of the outer layers of the periosteum as a "limiting membrane" is in part overthrown by these tumors in their outward growth. The fact, however, that they do not grow in an irregular manner but maintain a more or less smooth domelike shape is perhaps evidence of the presence of a partially "limiting membrane." On the other hand, the endocranium (outer dural layer), which is not involved in these tumors, appears to demonstrate more definitely its function as an internal "limiting membrane," by preventing any marked growth of the tumor toward the intracranial cavity. The resistance of this membrane, however, also frequently gives way before the severe pres-

15. Axhausen, George: Arch. f. klin. Chir. **88**:23, 1908-1909.

16. Haas, S. L.: The Importance of the Periosteum and the Endosteum in the Repair of Transplanted Bone, Arch. Surg. **8**:535 (March) 1924.

17. Haller, quoted from Haas.[16]

18. Hunter, John: Collected Works, London, James F. Palmer, 1837.

19. Goodsir, John: Anatomical Memoirs of John Goodsir, William Turner, 1868.

20. MacEwan, William: The Growth of Bone, Glasgow, James Maclehose & Sons, 1912.

21. Stump, C. W.: Histogenesis of Bone, J. Anat. & Physiol. **59**:136, 1925.

sure of an osteoma of the orbit or frontal sinus, as it does when an osteoma arises on the inner table.

Poirrier [22] suggested the possibility of the cranial sutures as a site of origin for these osteomas, but advanced no evidence in favor of this theory. The fact that active bone formation takes place in these

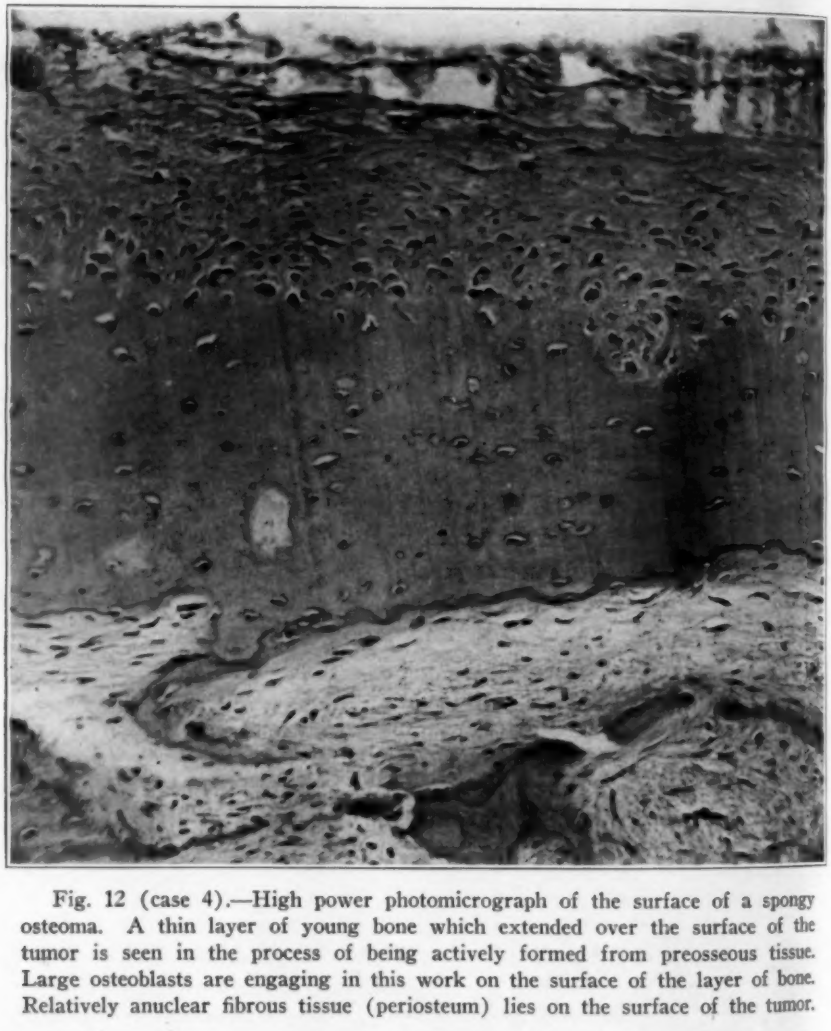

Fig. 12 (case 4).—High power photomicrograph of the surface of a spongy osteoma. A thin layer of young bone which extended over the surface of the tumor is seen in the process of being actively formed from preosseous tissue. Large osteoblasts are engaging in this work on the surface of the layer of bone. Relatively anuclear fibrous tissue (periosteum) lies on the surface of the tumor.

regions often until late in life certainly makes them a suspicious site, but although some osteomas may arise from them, others have been

22. Poirrier, A.: Des exostoses ostéogéniques de la voûte du crâne, Paris, 1895, no. 433.

definitely shown to arise far from the suture lines. Even if some osteomas do arise from the sutures, there is no evidence to disprove that they arise in the periosteal region in these locations.

In referring to the age incidence of these tumors, it was remarked that approximately 50 per cent of them arose before the patient was 8 years of age and about 75 per cent before the twelfth year. These observations prove of significance when the growth of the skull bones is investigated. In Quain's [23] book on anatomy is found the following:

> The skull grows rapidly during about the first seven years of life. By that time certain parts including the circumference of the occipital foramen, the body of the sphenoid, the cribriform plate and the petrous portion of the temporal have attained their definitive size. The other regions also increase, but little, until the approach of puberty when a second period of active growth begins affecting especially the face and the frontal portions of the cranium, with which is associated the expansion of the frontal and other air sinuses—the frontal sinuses appear about the seventh year and continue to increase in size up to old age.

Since the large majority of osteomas arise during the active period of the growth of the skull, it is logical to believe that the production of these lesions is more favored in growing than in nongrowing bone. This early age of onset was noted in osteochondromas by Geschickter [6] and in the osteomas of the frontal sinus by Armitage,[24] who claimed that 50 per cent arise during adolescence. The literature seems to indicate that even more than 50 per cent of the osteomas of the frontal sinus arise before puberty, for although they may not be recognized until later, it is necessary to realize that they usually must attain a considerable size first.

The next question that confronts one is, Why should approximately 60 per cent of the osteomas involve the frontal bone and 50 per cent be almost totally restricted to this bone? It is known how comparatively common are the osteomas of the facial bones and of the frontal sinus of which Armitage [24] collected 119 from the literature. When one recalls that the frontal and facial bones continue to increase in size for a considerable time after many of the other bones have ceased to do so, and also that they show a special acceleration of growth about puberty, it becomes apparent that there may be some relation between these phenomena. Perhaps an osteoma in a bone which continues to grow actively for a long time is more likely to reach a larger size and hence to become clinically apparent than is an osteoma in a bone which grows sluggishly or ceases to grow at an earlier period. It is known that osteochondromas usually cease to grow when the bone of which they are a

23. Quain, Jones: Elements of Anatomy, ed. 10, edited by Schäffer and Thane, London, Longmans, Green & Co.; 1890-1895, vols. 1 and 2.

24. Armitage, George: Osteoma of the Frontal Sinus with Particular Reference to Intracranial Complications, Brit. J. Surg. **18**:565, 1931.

part ceases to do so, but unfortunately it is not known whether most of them would not have stopped growing regardless of whether the bone did so or not.

Another contributing factor is that if the production of an osteoma is more favored in growing bone then there is a longer period during which osteomas might arise from the frontal and facial bones than from bones ceasing to grow at an earlier date. The fact that the face and the frontal regions are perhaps more subject to trauma and that infection is more prevalent in these regions may also be factors in the production of the growths.

In the foregoing analysis, the osteomas appeared to arise either from the periosteum or subperiosteally on the surface of the skull. The larger osteomas were of the spongy type showing in their development a spongy transformation or absorption of the outer table and an eventual deposit of a layer of bone on their surface, and in some cases a quiescent end-stage or eburnated structure. Other osteomas, particularly those arising in adults, appeared to remain of a more or less eburnated character from the beginning. These phenomena are of particular interest when one consults those who have observed the healing of fractures. Although less callus is formed at the site of a fracture of a cranial bone and the union is more often a spongy one, the resultant process of healing is essentially similar to that in a long bone, when no intermediary cartilaginous stage occurs. In support of this, Dr. Dandy stated that he had observed solid bony union in some of his cranial osteoplastic flaps. At the site of a fracture, as is well known, after the original blood clot has been absorbed and replaced by granulation tissue, there occurs a formation of young bone trabeculae "which are first seen under the stripped periosteum in its angle of junction with the bone" (Leriche and Policard), and which spread out into the mass of fibrous tissue between the fractured ends of the bone to form a spongy callus. Coincident with the first of the foregoing phenomena, there occurs a process concerning which Leriche and Policard [25] wrote:

> Biologically the most essential phenomenon, though histogenetically unobtrusive, is constituted by the slow but progressive resorption of bone at the extremities of the fracture. This resorption is manifested by the enlargement of the Haversian canals and of the connective tissue spaces. The bone disappears by osteolysis, much less than by osteoclasis. This disappearance always precedes the formation of new bone tissue. One can therefore say that the genesis of new bone trabeculae seems to be conditioned by the resorption of preexisting bone.

Here, then, is a probable explanation of the absorption or spongy transformation of the outer table as well as the inner table of the skull.

25. Leriche, R., and Policard, A.: The Normal and Pathological Physiology of Bone: Its Problems, translated by S. Moore and J. A. Key, St. Louis, C. V. Mosby Company, 1928.

Following the foregoing stage in the repair of a fracture, there occurs a resorption of the spongy callus in its more central areas with reformation of the medullary canal or diploe, a gradual formation of cortical bone continuous with the old cortical bone of the shaft or outer table and the return of the periosteum to its former relationship. This seems to explain the deposit of a bony shell over the spongy osteomas.

Concerning the healing of fractures, MacCallum [8] wrote: "The osteoid tissue may be laid down as a solid layer on the surface of the old bone or through the guiding action of the blood vessels assume a spongy form. Solid new formed tissue of this kind may be transformed later into spongy bone by the invasion of the blood vessels and that in turn become compact by later growth." Thus again is seen that the development of an eburnated or a spongy osteoma in part at least represents an exact replica of the normal growth of bone, but that some imbalance between the various processes concerned occurs with the resultant formation of an osteoma. From this it is not argued that all osteomas are due to trauma, although a fracture through the outer table with coincident imbalance of the factors concerned in repair could well explain their origin, as it is possible for the growth impetus to arise in the bone from many poorly understood sources, including periosteal infection. To say that these osteomas arise spontaneously is merely an admission that they arise from some obscure cause, as is also the case when one is forced to use the word imbalance.

Osteomas showing no clinical change in the outer table of the cranium occasionally extend toward the intracranial cavity from the inner surface of the skull and cause pressure on the brain. They apparently arise from the endocranium, or subendocranially. It is possible that osteomas may at times arise from the diploe, but no example of this type has been found.

The fundamental pattern of ossification observed in this study for osteomas of the cranium characterized by subperiosteal bony growth with accompanying spongy transformation of underlying bone is also typical for similar new growths arising in other membranous bones. A subsequent study of similar lesions of the jaws was suggested by Dr. Geschickter. This was undertaken (Geschickter and Echlin), and a similar histogenesis in so-called central fibromas and central fibrosarcomas, as well as osteomas, was demonstrated. These benign ossifying lesions, like the cranial osteomas, arise subperiosteally and are characterized in the roentgenogram by a spongy transformation of membranous bone extending outward from which is a smoothly outlined dome. On the surface of this dome is sometimes present a shell of newly formed bone. These growths often appear to be central because of the continuation of underlying spongy bone with the body

of the tumor as well as the presence of a bony shell on their surface. This bony shell has often been mistaken for the expanded cortex of the underlying bone. When the facts gathered from the study of the pathology and histogenesis of cranial osteomas as reported in this paper are considered from this larger point of view, including the similar ossifying lesions in other membranous bones, it seems justifiable to class the osteomas of membranous bones as a distinct entity different from the exostoses (osteochondromas) in cartilaginous bones.

TREATMENT

Since many of the cranial osteomas grow slowly and remain small, operative intervention is not always indicated. If a spongy osteoma, however, is increasing in size, it seems wise to remove it and thus avoid a possible thickening and slight depression of the inner table.

Unless osteomas are completely removed, they tend to recur. In one case, however, although only the outer portion of the tumor was removed, the inner table being left intact, the osteoma did not recur except at one portion of its periphery (case 5).

HISTORICAL

Although isolated cases of osteomas of the cranial surface had appeared in the literature prior to 1863, Virchow [7] in this year presented the first comprehensive work on the subject. He described the osteoma as passing from an original spongy stage to an eburnated stage, and finally perhaps to a spongy stage again. The spongy type, he believed, showed a continuation of the cancellous bone with the diploe. In speaking of osteomas of the skull in general, including osteomas of the sinuses and orbit, he wrote, "and scarcely do they belong to a single category, a part of them in my opinion belong to the enostoses, another part to the exostoses and a third to the chondromata."

Prengreuber,[26] in 1892, believed that exostoses of the cranium were never solitary, but coexisted with multiple exostoses.

In 1895, Poirrier [22] disagreed with Prengreuber. He deplored the state of confusion that existed in the classification of these growths, stating that until that time syphilitic, tuberculous and other lesions were all included under the heading of osteomas. He believed that they were solitary lesions independent of any other skeletal growth, but that they were more frequent in the female sex. He thought some of them might have arisen from the suture lines or from a wormian bone, but gave no substantiating evidence in favor of these theories. He wrote, "they are most common on the surface of the cranium and are usually eburnated, but may pass through a cartilaginous stage." He

26. Prengreuber, M., quoted by Marey.[9]

was quoting Virchow's theory of chondromas when he spoke of a cartilaginous stage, never having observed it himself. As has been pointed out, osteochondromas may rarely arise from cranial bones preformed in cartilage, but are quite different tumors from the osteomas described.

Marey,[9] in 1910, again stated that the osteomas of the skull had been somewhat neglected in the literature. He believed that "the cranial osteomata are not a pathological rarity. Contrary to the classical opinion, it is not a lesion occurring particularly in females and is able to co-exist with exostoses of the other bones." In his paper he included a case of Nageotte's which has been left out of this one. The patient, aged 15, since the age of 8 years had had exostoses of the frontal scapular and tibial bones with accompanying anemia and fatigue. Marey also wrote, "It seems legitimate to put in a group by themselves the spongy exostoses 'spongiostéomes' which are characterized by their faint density, their transparence in the x-ray and their tendency to develop not only toward the exterior, but also toward the interior of the cranium." He apparently believed that the spongiostéomes were a different type of lesion from the eburnated ones. He presented only one new case. The patient had a spongy osteoma, and epileptic seizures developed fifty-three years after the onset of the tumor. This case was included in the present study. It is true that in the spongy osteomas the inner table of the skull sometimes becomes transformed into spongy bone and slightly depressed, but in the foregoing analysis it was shown that the spongy and eburnated osteomas are only different manifestations of the same process.

Luxembourg [27] wrote a paper on this subject in 1918 and claimed that he was able to find little of value concerning the osteomas in the literature. Some of the osteomas in the literature he described as developing inwardly and outwardly. The only case with signs of increased intracranial pressure contained in his paper, however, was one reported by Hauff in 1846 and appeared to have been a hyperostosis over a meningeal fibroblastoma.

Orator,[10] in his paper in 1931, briefly reviewed the German literature on cranial osteomas and presented one new case. He concluded that the osteomas of the tabular bones arise early in life and are much more frequent in females than in males. He divided them into spherical and penetrating types, but did not recognize a transformation of one type into another, nor did he have anything to say concerning their origin. His own case he placed in the penetrating group. In the present paper it was grouped with the large spongy osteomas resting on a thickened and somewhat depressed inner table. In Orator's case

27. Luxembourg, H.: Beitrag zur Kenntnis der Osteome des Schädeldaches, Deutsche Ztschr. f. Chir. **147**:256, 1918.

the neurologic examination gave negative results. The osteoma in one of his cases (previously reported by Eiselberg) apparently arose from the frontal sinus, and in another multiple osteomas were present.

In 1931, Armitage [24] wrote, "Osteomata of the frontal sinus as is almost invariably the case with bony tumors growing in connection with the cranial bones are of the hard, ivory compact variety—so-called exostoses eburnea." As was pointed out in this paper, the majority of the large osteomas studied were of the spongy type.

CRANIAL HYPEROSTOSES PRODUCED BY MENINGEAL FIBROBLASTOMAS

INTRODUCTION

The fact that meningeal fibroblastomas (meningiomas) frequently produce hyperostoses of the overlying cranium is now well recognized. The confusion that at times exists in the clinical and roentgenographic differentiation between these hyperostoses and the osteomas of the external surface of the cranium has prompted this portion of the paper.

With regard to the origin of the meningeal fibroblastomas, Penfield [28] wrote, "It must therefore be concluded that these tumors may arise from any portion of the meninges, but that they most frequently derive their origin from arachnoidal tufts, growing into and being vascularized by the dura." Concerning their subsequent growth, Cushing [29] remarked that they may form themselves into "massive tumors with a relatively small area of meningeal attachment" or into "tumors en plaque which are but slightly elevated, though they may involve a considerable area of dura."

Coincident with this growth there may occur changes in the overlying skull, evidenced first by a hypervascularization and then perhaps by a partial erosion or proliferation of new bone, "most striking on the internal and external surfaces of the skull, where it is easily distinguishable as layers of new bone superimposed on one another" (Kolodny [30]). Regarding the changes in the skull, Phemister [31] remarked "the inner and outer tables were slightly more spongy than normal. The new bone both internally and externally, radiated from the surface of the old bone." Cushing expressed the belief "that at least 25 per cent of the endotheliomas are accompanied by an overlying

28. Penfield, W.: Tumors of the Sheaths of the Nervous System, in Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, p. 954.

29. Cushing, H.: The Meningiomas (Dural Endotheliomas): Their Source and Favoured Seats of Origin, Brain **45**:292, 1922.

30. Kolodny, A.: Cranial Changes Associated with Meningioma "Dural Endothelioma," Surg., Gynec. & Obst. **48**:231, 1929.

31. Phemister, D. B.: The Nature of Cranial Hyperostoses Overlying Endothelioma of the Meninges, Arch. Surg. **6**:554 (March) 1923.

hyperostosis cranii which is either palpable externally or demonstrable by the roentgen ray."

A microscopic examination of the hyperostosis resulting from this process, as has been revealed by all the foregoing authors, shows in most cases that it has been passively infiltrated with the cells of the meningeal tumor.

In speaking of the hyperostoses, Phemister [31] wrote:

> In the second case nervous symptoms were entirely absent and the hyperostosis was the sole complaint. Such cases as the latter have not infrequently been diagnosed as sarcoma or osteoma of the skull and the underlying tumor overlooked. This has happened even when evidences of brain compression were present as the internal hyperostosis was held responsible for the compression.

CLINICAL FEATURES

An analysis of the most important clinical features in patients with hyperostoses overlying meningeal fibroblastomas is presented. The analysis is made from a review of nine cases of hyperostoses produced by meningeal fibroblastomas found in this laboratory and eighteen similar cases reported in the literature and is constructed with the view of differentiating between these tumors and the osteomas previously discussed. Of the nine cases found in the laboratory, only five presented clinically recognizable hyperostoses; in the other four these were found at operation. The cases taken from the literature were not selected, but all the cases presented in the articles of Phemister,[31] Penfield,[32] Cushing,[33] Rand,[34] Cope,[35] Winkelman,[36] and Crowe and Jones [37] were used.

Seventeen patients in this series were males and ten were females. The age of the patient when the meningeal tumor first manifested itself is given in twenty-five cases. The average age of these patients was 31 years, only four of them being under 29 years at the time of onset of signs or symptoms. The patient presented by Crowe and Jones was 5 years of age when a bony tumor of the frontal bone was noted. It

32. Penfield, W.: Cranial and Intracranial Endotheliomata, Surg., Gynec. & Obst. **36**:657, 1923.

33. Cushing, H.: The Cranial Hyperostoses Produced by Meningeal Endotheliomas, Arch. Neurol. & Psychiat. **8**:1 (Aug.) 1922.

34. Rand, C. W.: Osteoma of the Skull: Report of Two Cases, One Being Associated with a Large Intracranial Endothelioma, Arch. Surg. **6**:573 (March) 1923.

35. Cope, Z.: Case of Frontal Endothelioma with Hyperostosis Cranii (Pacchionian Tumor?), Brit. J. Surg. **12**:794 (April) 1925.

36. Winkelman, N. W.: Hyperostosis and Tumor Infiltration of the Base of the Skull Associated with Overlying Meningeal Fibroblastoma, Arch. Neurol. & Psychiat. **23**:494 (March) 1930.

37. Crowe, S. M., and Jones, C. K.: Large Hyperostosis of Cranium Due to Arachnoid Fibroblastoma, Tr. Chicago Path. Soc. **12**:340 (June) 1927.

is possible that this patient had a cranial osteoma and not a hyperostosis overlying a meningeal tumor.

The average duration of signs or symptoms at the time of operation among these patients was five years.

Of the twenty-seven cases, the hyperostoses were reported as localized chiefly to the frontal bone in ten and to the parietal bones in four. In five cases the tumor was described as involving the frontoparietal region and in four cases, the temple or temporal fossa. In two of the four cases, the orbital plates became thickened with resultant unilateral exophthalmos. In the remaining four cases the tumor involved the vertex, the crown, the occipital and the temporo-occipital region, respectively. The fact that the majority of these tumors involved the frontal or parietal bones with the predominant number involving the frontal bone is perhaps significant, as will be pointed out later.

In fourteen cases, or approximately half of the total number studied, a symptomless hyperostosis presenting on the external surface of the skull was the first indication of disease noted by the patient. Only two of these patients were under 29 years of age when the hyperostosis first appeared, one being 24 and the other, the patient of Crowe and Jones, 5 years. It is in this group particularly that difficulty has arisen in making a differential diagnosis between a hyperostosis of the meningeal type, an osteoma, an osteogenic sarcoma and a hyperostosis of definite inflammatory origin. The average duration of the hyperostosis before symptoms arose in these fourteen cases was four years, but in four cases the bony tumor was the only manifestation of disease for over nine years.

The symptoms complained of by these fourteen patients after the appearance of the hyperostosis varied considerably according to the location of the lesion. Headache, often localized to the tumor, was the most common symptom. Pains about the lump, dizziness and failing vision were frequent. Partial hemiplegia developed in four of the cases, epilepsy in three and loss of memory with mental dulness in some cases, particularly in those in which the frontal lobes were involved. Unilateral exophthalmos was noted in two cases. In only one case was the patient operated on before symptoms arose, and this patient had had a large hyperostosis of the frontoparietal region for two years. The average duration of symptoms at the time of operation in this group was three years and of the hyperostosis eight years.

There are three other cases that could perhaps be included in the aforementioned group in which symptoms followed the appearance of hyperostosis. Hyperostosis developed in each of the three patients from one to two and a half years before operation, but one had had neuralgic pain in her head for seven years prior to operation, another a prominence of the left eye for ten years and the third pain in the right eye for ten years.

There were four patients in whom signs and symptoms of intracranial damage developed simultaneously with the appearance of hyperostosis, and finally, six with definite signs of an intracranial tumor in whom hyperostoses cranii were found only at operation or autopsy.

The hyperostoses varied in size from that of an acorn to that of a grape-fruit and were firmly attached to the skull, shading imperceptibly into it. In most cases they were semispherical, smooth or slightly lobular and bony hard, but in four cases they could be slightly compressed. Some tenderness on pressure over the bony boss was present in four cases. Dilated vessels in the scalp were mentioned in a few instances, and in one case the scalp was not freely movable over the hyperostosis, having been invaded by tumor cells.

General physical and neurologic findings varied greatly according to the amount and area of cerebral damage.

ROENTGENOGRAPHIC FEATURES

Roentgenographic changes in the cranium, the result of its infiltration by the cells of meningeal tumors, have been discussed by Heuer and Dandy,[38] Cushing,[33] Phemister,[31] Rand,[34] Sosman and Putnam,[39] Kolodny,[30] Camp,[40] Elsberg and Schwartz [41] and many others. The following brief description of these changes is included here to facilitate a comparison between cranial osteomas and hyperostoses produced by meningeal fibroblastomas and is mostly taken from the observations of the aforementioned authors.

As a result of a meningeal tumor, there may develop in the overlying cranium a hyperostosis, an erosion, a hypervascularization or a combination of all three processes.

When erosion of the skull is absent, the hyperostoses produced by these tumors are usually typical. Roentgenograms of cross-sections of the hyperostoses show their essential features most satisfactorily. Some excellent examples of this type are contained in the articles on this subject by Kolodny and Phemister, and similar features are borne out in the gross specimens presented by other authors. Fully developed hyperostosis is largely formed by new bone of a spongy character, arranged so as to radiate outward from both tables of the skull (figs. 13 and 14). The formation of new bone is usually more pro-

38. Heuer, G. I., and Dandy, W. E.: Roentgenography in the Localization of Brain Tumors, Bull. Johns Hopkins Hosp. **27**:311, 1916.

39. Sosman, M. C., and Putnam, T. J.: Roentgenologic Aspects of Brain Tumors: Meningiomas, Am. J. Roentgenol. **13**:1, 1925.

40. Camp, J. D.: The Roentgenologic Manifestations of Intracranial Disease, Radiology **13**:484, 1929.

41. Elsberg, C. A., and Schwartz, C. W.: Increased Cranial Vascularity in Its Relation to Intracranial Disease, Arch. Neurol. & Psychiat. **11**:292 (March) 1924.

Fig. 13 (courtesy of Dr. D. B. Phemister).—Roentgenogram of a cross-section through a hyperostosis produced by a meningeal fibroblastoma (meningioma). The outline of the skull is preserved, although the bone is spongy. Bone is seen to be laid down in two different planes; adjacent to the cranial tables it is deposited in strips parallel to the skull surface, thus preserving the skull outline; more peripherally, it radiates at right angles to the skull. Unlike the osteomas, bone is deposited on the intracranial surface of the inner table.

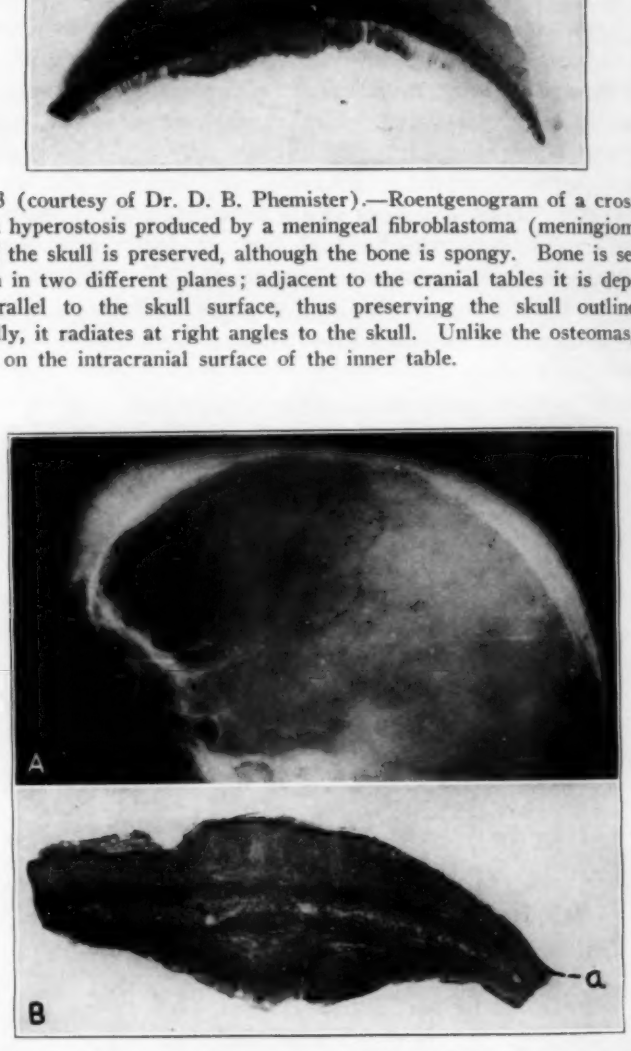

Fig. 14.—*A* (courtesy of Dr. J. D. Camp), roentgenogram of a hyperostosis caused by a meningeal fibroblastoma (meningioma). Spicules of bone are seen radiating from the outer surface of the frontal bone. The outline of the skull tables is faintly visible in the hyperostosis. New bone is present on the intracranial surface of the inner table. Stereoscopic plates should be used in order to more clearly visualize the inner table. Note the increased cranial vascularity.

B (courtesy of Dr. D. B. Phemister), roentgenogram of a cross-section of a hyperostosis produced by a meningeal fibroblastoma (meningioma). Note the widening and spongy transformation of the skull, the outline of which is well preserved. A large quantity of bone has been deposited on the under as well as the outer surface of the cranium.

nounced on the surface of the outer table than on the inner and presents a moundlike swelling passing at its periphery imperceptibly into the cranium. The outline of the cranium can be seen passing through the tumor. Concerning the hyperostosis, Kolodny [30] wrote, "even in the advanced cases of cranial changes, one may easily distinguish the outlines of both tables microscopically as well as in a radiogram of a slice of the removed bone flap. Destruction of the new formed bone on the intra-cranial side of the skull may lead to irregular, jagged excrescences of bone surrounded by soft tumor."

In a fully developed hyperostosis, although the outline of the cranium persists, it is usually widened both inwardly and outwardly, shows a spongy transformation with increased porosity and is rather hazy at the margins of the old tables. In contrast with the osteomas, the reason why the outline of the skull is still visible, even in the presence of a spongy change, is that new bone can be seen in the roentgenograms of some of the cross-sections of the hyperostoses to be laid down in two different planes. Proximal to the old skull tables the bone is laid down in layers parallel to the cranial surface, but more peripherally it is laid down at right angles to it (figs. 13 and 14 *B*). Microscopically this method of new bone formation is even more apparent.

In the early stages of development of a hyperostosis, and sometimes in elderly people, the skull may show only a slight thickening with no new bone radiating from it. The original thickening is the result of the deposit of bone in layers parallel to the surface of the skull. Below it one sees that the radiating spicules occur as soon as the periosteum is more completely stripped from the skull. Erosion of the skull sometimes takes place from within outward, either before or after the occurrence of hyperostosis (fig. 15). Hypervascularization, evidenced by widening of the haversian canals, is very common. Heuer and Dandy, as early as 1916, described some excellent examples of this type. Calcification is occasionally seen within the intracranial tumor, but this is apparently rare. A tumor of the soft part with perhaps an irregular layer of new bone on its surface can sometimes be visualized overlying the hyperostoses and at times may be the predominant feature (fig. 16). In some cases the meningeal tumor melts away the overlying skull like ice and presents as a firm, outwardly pulsatile swelling through the cranium. Dandy recently had such a case. Penfield [28] placed this type of meningeal tumor in the sarcoma group. Craig [42] endeavored to grade meningiomas according to their invasive properties, but this question will not be discussed here.

42. Craig, W.: Malignant Intracranial Endotheliomata, Surg., Gynec. & Obst. 45:760, 1927.

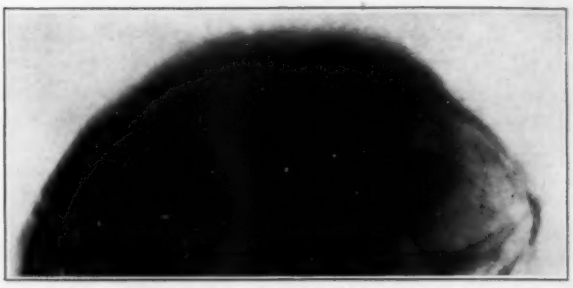

Fig. 15 (path. no. 45782).—Roentgenogram of a hyperostosis produced by a meningeal fibroblastoma (meningioma). Note the spicules of bone radiating from the surface of the skull. The outline of the cranium can be seen passing through the tumor. Some new bone is present on the under surface of the inner table, best seen on stereoscopic examination. Note the increased cranial vascularity and skull erosion.

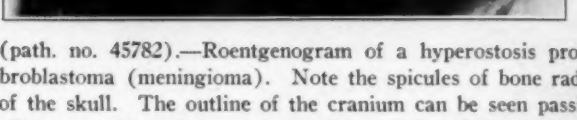

Fig. 16 (path. no. 37883).—Roentgenogram of a meningeal fibroblastoma (meningioma) presenting on the surface of the skull. New bone formation under the elevated periosteum is seen where the edge of the tumor merges into the skull. An irregular interrupted layer of bone is laid down on the tumor surface. A few thin strips of new bone are laid down at right angles to the skull parallel to the vessels in the tumor. Little or no bone radiates from the outer surface of the skull. The outline of the skull is well preserved. This patient was 54 years of age. A tumor had been present on the surface of his skull for eight years before the film was taken. This tumor can be easily distinguished from an osteoma by the intactness of the outer table of the skull, etc. The tumor was somewhat compressible.

GROSS PATHOLOGY

The gross specimens of the hyperostoses cranii over meningeal fibroblastomas reveal that bone described as radiating from the two tables is of the spongy type and is usually most abundant on the surface of the skull. In a few cases, and particularly in those in which erosion of the skull has commenced, little or no bone is found projecting from the inner table, but the rule, however, appears to be for it to do so when hyperostosis of any appreciable size is present. The cranium itself is also of a spongy nature when the hyperostosis is large, but its outline nevertheless persists.

Attached to the meninges beneath the hyperostosis lies the meningeal fibroblastoma which is invading the skull. It may either be of the spherical type with a small area of meningeal attachment or lie *en plaque* and be attached to the meninges over a considerable area. Although these tumors invade the skull, they are inwardly encapsulated, and usually destroy the brain only by pressure.

"On the outer surface of the bone is usually a pad of tumor," which "sometimes invades the overlying scalp and may infiltrate the temporal muscle when that is adjacent" (Penfield [28]). At times there may be little or no hyperostosis, but an enormous semispherical tumor of meningeal origin may lie on the surface of the skull (fig. 16).

MICROSCOPIC FEATURES

Microscopically, these hyperostoses are found to be infiltrated with the cells of the meningeal fibroblastoma to a greater or less extent. It is largely due to the infiltration of the skull by the cells of the meningeal tumor that hyperostoses are formed. These cells in their proliferation extend through the haversian canals and intertrabecular spaces toward the surface of the skull and in some cases show infiltration of the overlying scalp.

In most cases toward the surface of both tables and particularly toward that of the outer one, new trabeculae of bone are seen to be laid down in strips, parallel to the surface of the skull (figs. 17 and 18). The area of cranium involved shows a widening of the haversian canals and intertrabecular spaces, which at times is marked and gives this portion of the hyperostosis a definite spongy appearance. In the early cases the skull may show considerable infiltration with tumor cells and yet may retain a bony structure approximating the normal. This is apparently not common, however, as the increased cranial vascularity, which is usually present, will, in itself, cause widening of the haversian canals and intertrabecular spaces with resultant additional porosity.

In a fully developed hyperostosis there is seen radiating from both surfaces of the portion of the hyperostosis described, namely, the cranium proper and especially from the outer surface, trabeculae of

Fig. 17 (path. no. 45483).—Photomicrograph of the surface of a hyperostosis produced by a meningeal fibroblastoma (meningioma). Note that new bone is laid down in two distinct planes. The bony spicules in the lower part of the picture lie parallel to the surface of the skull and cover a much wider area than is seen here. Note the tendency for the meningeal tumor to be arranged in cords.

Fig. 18 (path. no. 45483).—Photomicrograph of the inner table of the skull involved in the hyperostosis shown in figure 17. Note again that bone is laid down in two different planes. Bone radiates at right angles from the inner table into the intracranial cavity.

new bone arranged more or less at right angles to the plane of the surface of the skull (figs. 17 and 18). Extending outward as a prolongation of the newly formed trabeculae are delicate bundles of pink-

Fig. 19.—Roentgenogram of a cross-section of an eburnated osteoma arising on the cranial surface. This osteoma was recently found and was not previously mentioned in the paper. It was removed at autopsy from the parietal bone of a man, aged 66, who died from other causes.

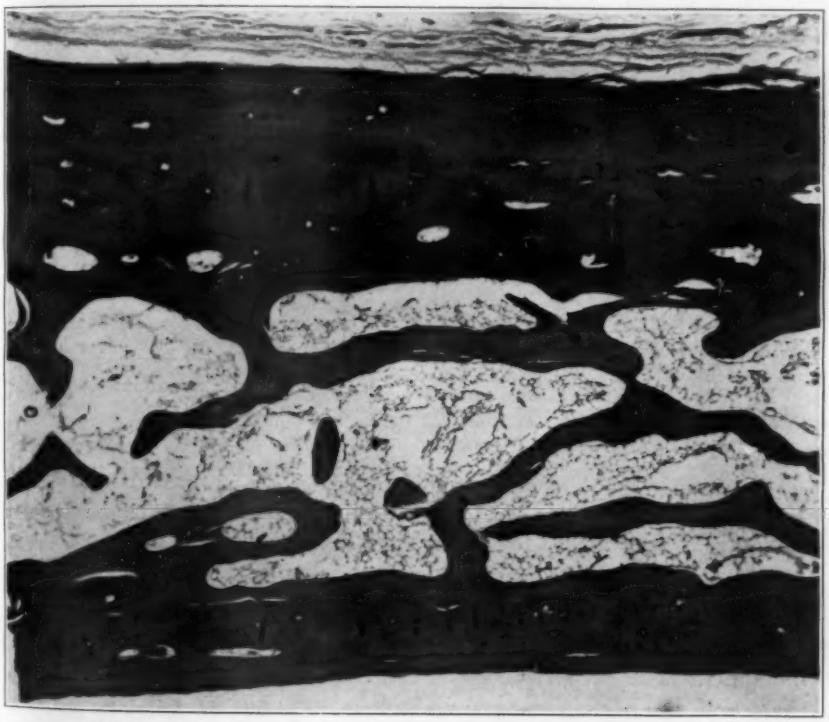

Fig. 20.—Photomicrograph of a cross-section of normal skull. Note the hyalinized periosteum on the surface of the skull. The outer table is thicker than the inner one. Compare this figure with the other photomicrographs.

staining fibers, identical in appearance to those observed by Quain [23] in ossifying embryonic membranous bone. (Compare the foregoing sections with figure 20, a microscopic section of a normal skull.) Cells

of the meningeal tumor lie between the newly formed trabeculae, and a pad of tumor is always formed on the surface of the outer table before trabeculae radiate from it.

There is no absolute line of demarcation between these two areas where bone is laid down in different planes, and this accounts for the haziness seen at their junction in the roentgenogram. These findings, however, explain why the outline of the cranium persists, even though it has undergone spongy transformation; and demonstrate one of the essential characteristics which clinically differentiate this type of hyperostosis from the cranial osteoma, in which, since the bone is not laid down in different planes, the outline of the skull proper is lost in the tumor. Normal-appearing osteoblasts always participate in the formation of the new trabeculae.

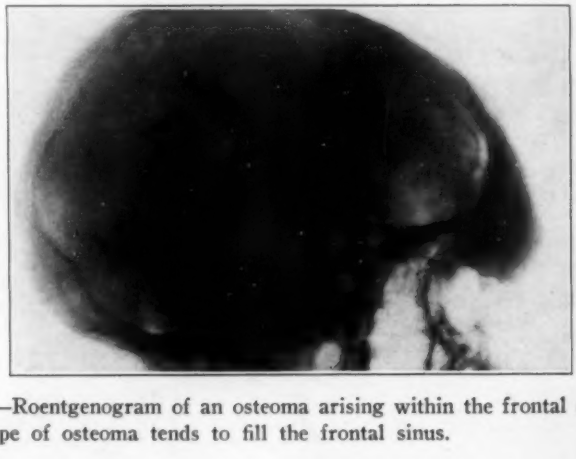

Fig. 21.—Roentgenogram of an osteoma arising within the frontal sinus. Note that this type of osteoma tends to fill the frontal sinus.

For a detailed description of the microscopic features of meningeal tumors, one may consult Penfield,[28] Cushing,[43] Weed,[44] Mallory,[45] Ewing [1b] and others. Here it is sufficient to say that the tumor cells are irregularly round or oval, sometimes being elongated, and that the nucleus contains abundant chromatin arranged in a netlike formation. The cytoplasm of the cell is voluminous, but the boundaries are usually indistinct. The cells resemble those seen in the pacchionian granulations and are often arranged in whorls, columns or clumps. In the

43. Cushing, H., and Weed, L. H.: Studies on the Cerebro-Spinal Fluid and Its Pathway: IX. Calcareous and Osseous Deposits in the Arachnoides, Bull. Johns Hopkins Hosp. **26**:367, 1915. Cushing.[29]

44. Weed, L. H.: The Cells of the Arachnoid, Bull. Johns Hopkins Hosp. **31**: 343, 1920. Cushing and Weed.[43]

45. Mallory, H.: The Type Cell of the So-Called Dural Endothelioma, J. Metab. Research **41**:349, 1920.

center of the whorl is frequently seen a hyalinized blood vessel, a clump of collagen, or a psammoma body (corpora amylacea). A fibrous tissue stroma may be scanty or abundant.

COMMENT

Leriche and Policard,[25] who have made an extensive study of the normal physiology of bone, throw some light on the changes observed in the skull as a result of increased vascularity which is so often an accompanying feature of meningeal tumors. They expressed the belief that "if by any process whatever, the activity of the circulation is increased in the vicinity of a bone, the latter becomes rarefied. It changes neither in chemical composition nor in its fundamental histologic structure. It changes only quantitatively in the relation to that of the connective tissue. The medullary canals increase and the bone trabeculae diminish. The architecture of the bone is modified, but not the chemical structure of the bone substance present in the tissue; in the bone trabeculae which remain, the structure and composition are the same; only the size and number are diminished." This rarefaction of the skull accompanying an increase in circulation has been observed by most authors who have studied the meningeal tumors, but it has not been so adequately explained as by Leriche and Policard.

They also wrote, "In some instances, the exact rôle of the circulatory activity may be masked. An increase of the circulation leads to bone resorption, but through the freeing of calcium and the creation of a local calcific excess, new bone can be formed. There will then be histological atrophy of the bone tissue and anatomical hypertrophy of the bone as a whole. This double process in hypertrophic resorption is extremely frequent. It dominates bone pathology. . . ." This last observation to some degree supports Kolodny's [30] belief, but in no way proves it, that "proliferation of bone precedes the infiltration of the bone by tumor cells. This proliferation follows on the heel of a local dilatation of the vascular channels in the skull." Later it is shown that although some thickening of the skull may be due purely to a hypervascularization of the bone, the majority of the hyperostoses are a direct result of invasion of the tumor.

It was noted in the roentgenograms and microscopic sections that new bone in the hyperostoses was laid down in two different planes. Other authors have observed this method of new bone formation in the hyperostoses, but have not sufficiently explained its mode of origin, nor have they noted that this is the main reason why the outline of the skull is preserved.

It is well known that the skull normally increases in thickness by "successive depositions of bony lamellae under the periosteum" (Quain [23]), and that a similar deposition of bone in layers parallel to the

surface of the cranium occurs when the periosteum "suffers minute elevations." This is just what happens when the meningeal tumor grows through the outer table of the skull and causes a periosteal elevation. The endocranium of the inner table at a later date also becomes stripped from its attachment when the tumor in its proliferation grows inward as well as outward. This perhaps explains in part why the hyperostosis is smaller on the inner table of the skull as the tumor cells first have to reach a subendocranial (subendosteal) location and then later in their multiplication grow down toward the intracranial regions. Another reason is that the periosteum (or subperiosteal tissue) is a more active bone-forming organ than the endocranium (or subendocranial tissue).

After the tumor cells have passed through or more completely stripped the periosteum from its attachment, a vascularized fibrous tumor of meningeal origin is formed on the surface of the skull. Into this tumor, small spicules of bone radiate at right angles from the surface of the skull as previously described. This type of ossification is explained by Geschickter and Copeland [6] in their discussion of Ewing's sarcoma of bone. They stated:

> Due to the growth of the tumor and subsequent hemorrhage, there is a gradual separation of the periosteum from the underlying cortex. Parallel deposits of new bone appear as a result of proliferation of the peripheral layer of the cortex when the periosteum has suffered minute separation. With increased separation of the periosteum, spicules of new bone from the subperiosteal regions are laid down at right angles to the shaft rather than parallel. We agree with Ribbert that this is due to the blood vessels perforating Volkmann's canals. After the separation of the periosteum, these vessels determine the direction of the new growth of bone when they are pulled outward in maintaining their continuity. The two types of formation of bone parallel and radiating, duplicate the process observed in the embryo, etc.

The same mode of new osseous deposit is seen to a lesser extent on the inner table, and the explanation for this is apparently similar.

Phemister,[31] in his paper on the hyperostoses under discussion, expressed the belief that "whether it [the new bone formation] arises from tumor cells or from the old bone, it is arranged to support the tumor." In support of this view, one may consult Phemister's article as well as Quain's [23] study of the growth of membranous bone. Quain said, "It may be observed that the appearance of the ossifying membrane bone in the shape of a network of trabeculae, seems to be determined by the preexistence of a vascular network in the embryonic tissue. The new bone everywhere makes its appearance in the spots which are furthest from the vessels, and the bony network everywhere alternates with the vascular network." Thus the radiating arrangement of the new bone formation is probably determined by the preexisting

vascular structure of the meningeal tumor which radiates from the surface of the skull (fig. 16).

Phemister [31] is also of the opinion that "the new bone (in the hyperostosis) is not tumorous in nature and is merely ossified stroma of the invading endothelioma." This opinion seems logical, especially perhaps in the light of experiments performed by Leriche, Policard and others, who have shown that any fibrous connective tissue in an embryonic state, when in apposition with bone, may undergo ossification if there is produced by hypervascularization and consequent rarefaction of the adjacent bone a local excess of calcium. Although Phemister's theory is logical, it must be remembered that some of the new bone formation in the hyperostosis is undoubtedly of periosteal or subperiosteal origin (fig. 16).

Another question that deserves consideration is, Why should so many of the hyperostoses involve the frontal bone? It has been shown by other authors that the majority of meningeal tumors arise from the meninges over the vault of the skull, and this has been explained by their possible origin from the pacchionian granulations, which are so frequent in this region. Although many meningeal tumors arise in regions nearer the base of the skull, hyperostoses in these regions are apparently very infrequent. It will be remembered that osteomas show a tendency to develop in growing bone. Hyperostoses may show this same tendency. In support of this supposition is the fact that the frontal bone not only continues to grow after many of the other bones have ceased to do so, but also shows a more active growth in later life than the other cranial bones. The parietal bone, which is also frequently involved, is likewise among the bones that continue to grow after many of the others have ceased to do so. It does not, however, show such an active growth as the frontal bone in later life.

DIFFERENTIAL DIAGNOSIS [46]

There are many essential differences between the benign osteomas of the outer surface of the cranium discussed in this paper and the hyperostoses produced by meningeal fibroblastomas, and although difficulty at times will be encountered in distinguishing between them, their differential diagnosis should as a rule be easy.

Evidence of increased vascularity and of erosion so frequently seen in the skull over meningeal tumors is an uncommon accompanying feature of osteomas. A spongy osteoma, however, occasionally appears to erode the skull, but this is due to its spongy nature. A lateral view of the tumor is therefore always indicated. Hyperostoses are more

46. The osteomas referred to in the first part of this differential diagnosis are, of course, the osteomas described in detail in this paper, namely, those that arise from the periosteal region on the cranial surface.

often tender than osteomas, and sometimes present a pad of tumor on their surface. Meningeal tumors frequently cause severe intracranial damage, but osteomas rarely do so. In a hyperostosis, the outline of the cranial tables persists. In an osteoma of any appreciable size, the outer table is absorbed. Bony spicules which so commonly radiate from both surfaces of the skull in the hyperostoses are only occasionally seen near the surface of the dome of an osteoma and rarely if ever radiate from the inner table underlying it. Apart from these general differences between the two tumors, osteomas show certain special differences according to the stage of their development.

The fact that osteomas usually arise before or about puberty, whereas meningeal tumors are most frequent in the fourth decade of life, eliminates more of the difficulty in differentiating between these two lesions. Rarely, however, osteomas occur in adults, but in these cases the tumors unlike the hyperostoses are more often eburnated, show a dense shadow in the roentgenogram and produce no radiating bony spicules from the inner or outer tables of the skull.

The spongy osteomas of long duration should give little trouble in diagnosis, as again, unlike the hyperostoses, they usually arise in youth or in infancy, show an absorption of the outer table of the skull, some depression and thickening of the inner table, but no new bone radiating from it, and frequently have a thin shell of bone on their surface.

The spongy osteomas may early in their growth show spicules of new bone radiating from the surface of the skull in a manner similar to that seen in the hyperostoses cranii. Since these osteomas apparently originate in the periosteal region, the inner table of the skull in their early stages should show no change from the normal. In the formation of a hyperostosis, the meningeal tumor usually causes an increased porosity of the inner table or the production of spongy bone radiating from it. A stereoscopic film should, therefore, be of value in distinguishing between the two lesions. The other points of differentiation mentioned should, as a rule, decide the diagnosis.

The thickening of the skull, which occurs in a hyperostosis before the formation of radiating spicules, may give a little difficulty, however, if the diagnosis is based on this criterion alone.

Low grade osteomyelitis of the skull may sometimes simulate either of the foregoing tumors, but in the roentgenogram the irregular areas of bone destruction with adjacent areas of sclerotic bone are usually typical.

Primary sclerosing osteogenic sarcoma may be recognized by the rapidity with which it produces a large area of bone destruction and irregular new bone formation. The radiating manner in which new bone is sometimes laid down occasionally resembles closely that seen in a hyperostosis fo meningeal origin. Other primary tumors of the

skull as well as metastatic ones are generally much more rapidly growing than osteomas or hyperostoses of meningeal origin. Most of them are destructive. The benign giant cell tumor, if subperiosteal in origin, is usually soft. If it arises in the diploe, it produces an expanding and destructive lesion.

The characteristics of osteochondromas of the cranial surface were pointed out (fig. 1). Osteochondromas growing intracranially are often hard to visualize in the roentgenogram and cause compression of the brain.

Osteomas of the orbit and frontal sinuses may in their growth cause a swelling of the frontal bone, but the fact that these tend to fill the orbit and frontal sinuses, respectively, differentiates them from the osteomas of the cranial surface which never do this (fig. 22). Osteomas arising from the inner table of the cranium usually cause early damage to the brain and rarely if ever produce a demonstrable clinical change in the outer table. Exostoses of syphilitic origin are frequently multiple and usually disappear rapidly with antisyphilitic treatment.

A biopsy is indicated when any doubt exists as to the nature of a cranial tumor.

CONCLUSIONS

1. The osteomas discussed in this paper may be either spongy or eburnated, and arise from preosseous tissue on the cranial surface, as a rule, early in life. They grow slowly and most frequently take origin from the frontal bones, although other cranial bones are also commonly involved. They usually, if not always, arise in growing bone.

2. In its growth the spongy type of osteoma usually causes an absorption or spongy transformation of the outer table of the cranium and becomes continuous with the diploe. As a result of this process, the inner table of the skull in the region of the tumor may become slightly depressed and thickened, but rarely sufficiently, unless a complicating factor is present, to cause compression of the brain. A layer of bone is sometimes laid down on the surface of the tumor. Microscopically, this bone is young in type and is being actively formed from preosseous tissue. It is not, therefore, as usually believed, the expanded outer table of the cranium. This type of osteoma has often been described as arising from the diploe.

3. The fundamental pattern of ossification observed in this paper for osteomas of the cranium, characterized by subperiosteal growth, with accompanying spongy transformation of underlying bone and the frequent deposit of a subperiosteal shell of new bone, is also typical for similar new growths arising in other membranous bones.

4. Osteomas of the cranial surface rarely arise in adults, and then tend to be of the dense eburnated type.

5. Osteomas of membranous bones are a distinct entity from exostoses (osteochondromas) in cartilaginous bones.

6. Hyperostoses produced by meningeal fibroblastomas can be distinguished from osteomas of the cranial surface prior to operation.

Osteomas usually arise in youth and hyperostoses in the fourth decade of life. Compression of the brain, so commonly an accompanying feature of hyperostoses, is rarely caused by osteomas unless some complicating factor is present. Hyperostoses are more frequently tender than osteomas and unlike osteomas are sometimes compressible.

The roentgenographic differences between these two bony growths are distinctive.

7. In the formation of a hyperostosis, ossification adjacent to the tables of the skull occurs in parallel strips under the periosteum and endosteum when these tissues are minutely elevated by the meningeal tumor in its growth. When these tissues become more completely stripped from their attachments, new bony trabeculae are laid down at right angles to the cranium, the direction of their deposit apparently being determined by the radiating vascular arrangement of the meningeal tumor. This deposit of trabeculae in two different planes explains why the outline of the cranium persists in the hyperostosis.

In the region of a meningeal fibroblastoma a small amount of thickening of the skull may result purely from hypervascularization, but the production of a hyperostosis of any appreciable size is apparently always due to the infiltration of the skull by the cells of the meningeal tumor.

8. Osteomas that cause severe pressure on the brain usually arise either about the paranasal sinuses or the orbit or from the inner surface of the skull and not in the periosteal region on the cranial surface.

REPORT OF CASES

CASE 1.—*History.*—A white man, aged 28, was admitted to Dr. Dandy's service on Sept. 8, 1920, complaining of a lump on the forehead. The family and personal histories were irrelevant.

At the age of 5 years, the child's parents noted a small lump in the center of his forehead about the size of a ten cent piece. This remained practically stationary until eight years before admission, when, as a result of trauma, it grew rapidly, reaching three times its former size in a few days. The tumor was incompletely removed in 1912 and 1914. It then recurred and grew slowly. There were severe headaches in the afternoon for several years, and a sense of pressure in the region of the tumor for a short period.

Physical Examination.—The patient was well nourished. The temperature and pulse were normal. The forehead presented an old postoperative scar in the midline under which was an uneven but smooth, rounded, bony hard, nontender mass, 8 by 3 cm. and protruding 1 cm. from the skull. The eyegrounds were normal. The general physical and neurologic examinations gave negative results.

There were 8,000 white blood cells and 100 per cent hemoglobin. A culture from the frontal sinuses taken at operation showed no growth.

Operation (Dr. Dandy).—The osteoma was removed with a surrounding margin of normal bone. Both frontal sinuses were opened, but appeared perfectly normal, except for enlargement. In the opinion of the operator, "the osteoma was probably due to a chronic inflammatory condition of the frontal sinuses."

The diagnosis at the time of operation was osteoma of the frontal bone, probably arising from the frontal sinus.

Gross Pathology.—The specimen consisted of a piece of bone, 7 cm. long, projecting from the flat outer surface on which were two rounded lumps fusing together. These were of bony consistency and fused imperceptibly into the surrounding skull. The undersurface of the inner table of the skull was smooth, and showed the median longitudinal ridge and no evidence of new bone formation.

Microscopic Pathology.—The section through the tumor showed a surface layer of hyalinized fibrous tissue with a layer of underlying cortical bone, which in turn fused with a zone in the center of the tumor of cortical bone showing wider intertrabecular spaces, and this finally gave place to a layer of cortical bone or inner table of the skull. The inner table was smooth and normal in appearance. There was no evidence of new bone formation in the section.

Ultimate Result.—Up to 1929, there had been no recurrence of the tumor, but the patient had had chronic frontal sinusitis.

CASE 2.—*History.*—A white man, aged 33, was admitted to the service of Dr. Dandy on June 12, 1920, complaining of a lump on the forehead. The family and personal histories were irrelevant.

In 1909, the patient was struck on the forehead by a pointed metal spike which penetrated the skin; the wound healed rapidly. In 1915, a lump appeared at the identical spot of the trauma and reached its present size in six months, but then remained practically stationary. The patient could feel a dent in the tumor at the site of the old trauma for some time. There were no symptoms referable to the tumor and no headaches, changes in vision or neurologic symptoms.

Physical Examination.—The patient appeared healthy; the temperature and pulse were normal. On the forehead, just over the left orbit, was a bony, hard, smooth, regular, nonmovable, nontender tumor, the size of a walnut. The skin over the tumor was freely movable and appeared normal. Pressure over the left frontal sinus disclosed slight tenderness. The remaining examination, including a neurologic examination, gave negative results. The Wassermann reaction was negative.

Operation (Dr. Dandy).—The tumor was chiseled off level with the skull. "It was bone, quite spongy with wide interstices." A wide margin of normal bone, including the inner table, was then removed.

A diagnosis of osteoma of the skull was made.

Gross Pathology.—The gross specimen consisted of three pieces of bone, each made up of a mass of cancellous bone and fibrous tissue with an overlying definite layer of fibrous tissue.

Microscopic Pathology.—The section through one of the pieces of bone showed a layer of hyalinized fibrous tissue on one surface. This fibrous tissue showed a gradual transition through a spindle cell stage to a definite preosseous tissue in its deeper layers. The preosseous tissue was very vascular and was actively laying down young cancellous bone.

Ultimate Result.—The patient was discharged well. On Oct. 30, 1931, he was reported well.

CASE 3.—*History.*—A white woman, aged 20, was admitted to the service of Dr. Dandy on May 25, 1921, complaining of headaches, a lump and pressure on top of her head. The family and personal histories were irrelevant.

At 1 year of age, she fell down a stairway and fractured her skull with immediate resultant internal strabismus and partial loss of vision in the left eye. Since then, she had had a lump on the right side of her head which grew slowly, but never showed any rapid increase in size. Following a "nervous break-down" three years before admission, she had a sense of pressure on top of her head. Tenderness over the lump was present for a few years, and for two months she had had severe pain and headaches beneath the tumor. Slight weakness of the left side had been present for some time. There was no vomiting.

Physical Examination.—The patient was a well nourished and intelligent woman. On the right side of the head at the junction of the frontal and parietal bones, encroaching on the midline and extending laterally for 8 cm., was a bony prominence, extremely hard and very tender near its lower margin. No cracked-pot sound was noted over the head. The vision was poor in the left eye, and the right disk was slightly injected. There was internal strabismus in the right eye, the tongue protruded slightly to the right, and there was slight weakness of the left arm and leg with exaggerated deep reflexes on the left. The remaining examination was negative. There were 6,020 white blood cells and 72 per cent hemoglobin.

Operation (Dr. Dandy).—Two openings in the vault of the skull were present. These were each 1 cm. in length, 0.5 cm. wide and about 3 cm. apart. The bone was extremely hard, but ragged, about the edges of these openings. Cerebrospinal fluid poured out through them. They were joined with rongeurs until a defect about the size of a silver dollar was made. Degenerated scarred cortex was seen. A large bone flap, the undersurface of which was slightly roughened, was then laid back. The dura was entirely lacking over the exposed area, and several round, smooth, apparently multilocular cysts containing clear fluid were present in the cortex. These were excised, and the bone flap was replaced. How much of the osteoma was removed is not known. Infection apparently played a part in this case.

A diagnosis of osteoma of the skull was made.

Gross Pathology.—There was no report.

Microscopic Pathology.—The section showed a loosely arranged, very vascular fibrous connective tissue, containing a few irregularly scattered bony spicules. This section was taken from the edge of the tumor.

Ultimate Result.—The patient was discharged well. On April 23, 1922, she was reported well.

CASE 4.—*History.*—A white youth, aged 19, was admitted to the service of Dr. Dandy on Sept. 22, 1931, complaining of a bony tumor behind the ear. The family and personal histories were irrelevant.

A small bony tumor was removed from behind the patient's ear in 1919. This tumor recurred and was removed in 1927. It again recurred and grew slowly, especially perhaps during the year prior to his admission. It was never painful or tender. There was no history of headaches, interference with hearing or otitis media. No other symptoms were complained of.

Physical Examination.—The temperature and pulse rate were normal. Behind the right ear and pushing it forward was a bony hard, nontender, slightly irregular tumor, 3 by 3 by 2.5 cm., attached to the temporal bone. The center of the mass lay about 4.5 cm. above the tip of the mastoid. The skin was normal and freely movable over the tumor, but there was present an old operative scar. The Wassermann reaction was negative. The general physical and neurologic examinations gave negative results. There were 10,400 white blood cells and 100 per cent hemoglobin.

Operation (Dr. Warthen).—The tumor was composed of a cancellous dome and a more compact base. It was removed with a small area of surrounding normal bone from the inner table, which was left intact.

A diagnosis of osteoma of the skull was made.

Gross Pathology.—A cross-section of the gross specimen consisted of several pieces of bone. On the surface of each was a layer of fibrous tissue, under which was a thin rim of fairly well calcified material and in the central portion what appeared to be cancellous bone.

Microscopic Pathology.—The section showed a layer of hyalinized fibrous tissue at the periphery of the section which passed through a fibrospindle cell stage and showed definite preosseous tissue in its deeper layers which was actively engaged in the formation of young, bony spicules. Underneath the surface layer of fibrous tissue was an almost continuous rim of young bone (being actively formed from preosseous tissue). Sections from the base of the osteoma showed a more quiescent picture and an abundance of adult cortical bone.

Ultimate Result.—The patient was discharged well.

Case 5.—*History.*—A white boy, aged 13, was admitted to the service of Dr. Dandy on Feb. 16, 1923, complaining of an enormous bony tumor in the frontal region. The family history and personal history were irrelevant.

At 7 months of age the patient's mother noticed a small lump, "the size of a pea," on the vertex of the child's skull. The lump was hard and nonpainful. It grew slowly in size until the patient was 4½ years of age, and then grew more rapidly, especially in the two years prior to admission. No pain, redness or tenderness was noted. Two years before admission, the patient's mother noticed two small lumps on either side attached to the nasal bone. These increased gradually in size, causing obstruction to breathing. The child never went to school, owing to the appearance of the deformity. He was somewhat mentally retarded. He had an irregular fever for four weeks prior to admission, the cause of which was unknown.

Physical Examination.—The patient was somewhat undernourished and showed slight mental retardation (the fact that he had not been to school might partially explain this). An enormous, bony hard, slightly irregular and faintly nodular, pear-shaped tumor, measuring 19 cm. in its anteroposterior diameter and raised 6.5 cm. from the surface of the skull was attached to the frontal bone and extended backward to about the parietal suture line. Its anterior border involved the glabella of the frontal bone and the left supra-orbital arch. There was no cracked-pot sound over the skull, nor was there tenderness. The skin was normal. The tumor seemed to fade imperceptibly into the surrounding skull. A small tumor mass was attached to the nasal bones in each nostril. There was a slight bony, nodular and roughened area on the surface of the third rib in the midclavicular line. The fundi were normal. Neurologic and general examination gave negative results

except for two or three fibrous-like nodules in the skin of the face and ear. There were 8,100 white blood cells. The Wassermann reaction was negative. A culture from the frontal sinus opened at operation showed no growth.

Operation (Dr. Dandy).—The osteoma was chiseled away, leaving the inner table intact. The surface of the tumor was formed "by a thin layer of bone, not more than 0.25 cm. in thickness, and below this was cancellous bone. A perforator, passing through the cortex, entered soft mushy bone through which it plunged easily. The left frontal sinus was opened and leveled down. It was of tremendous size and protruded beyond the normal curve of the frontal region, but showed no sign of infection. The right sinus was not opened."

The diagnosis was osteoma of the skull.

Gross Pathology.—The gross specimen consisted of several pieces of bone, each showing a hard, cortical surface with underlying cancellous bone.

Microscopic Pathology.—The section showed a layer of thick fibrous tissue overlying a thin continuous layer of young bone. The central areas of the tumor were composed of preosseous tissue and irregularly arranged trabeculae of young bone.

Ultimate Result.—The patient was discharged well. On March 20, 1930, he was in good health, but thought that the tumor was recurring over the right eye.

CASE 6.—*History.*—A white girl, aged 18, was admitted to the service of Dr. Dandy on Feb. 5, 1928, complaining of a bony swelling of the frontal region.

Since the age of 6 years, the patient had had a lump on the forehead and on the bridge of the nose. There was an indefinite history of having fallen out of a tree at this time and striking her forehead. She also had had a lump on the vertex of the cranium since birth. Both lumps grew slowly and regularly in size. There had been no pain or other symptoms.

Physical Examination.—The patient appeared healthy. The temperature and pulse rate were normal. On the forehead just to the left of the midline was a smooth, rounded, bony hard tumor attached to the skull. It extended upward to within 2 cm. of the hair line. Another similar prominence saddled the nasion, and there was a third, the largest, on the skull, in the midline just back of the hair line which was about 6 cm. in diameter and 2 cm. high. All these masses fused into one another. The skin was normal and freely movable over them. They were nontender. The results of the general physical and neurologic examinations were negative. The Wassermann reaction was negative. There were 9,100 white blood cells and 95 per cent hemoglobin.

Operation (Dr. Hart).—A very firm cartilaginous-like tumor was dissected off from the bridge of the nose (the cartilaginous appearance was due to the thick fibrous tissue on the surface of the tumor). In attempting to remove the remainder of the osteoma, an enlarged frontal sinus was opened. The operation was abandoned.

A diagnosis of osteoma of the skull was made.

Gross Pathology.—The gross specimen consisted of three small fragments of bone; each fragment was covered by a dense white fibrous tissue.

Microscopic Pathology.—On two edges of the section was seen dense, hyalinized fibrous tissue which in a few areas showed a gradual transformation to preosseous tissue in its deeper layers. This fibrous tissue overlay dense adult cortical bone which in places, however, was being added to from the areas of preosseous tissue mentioned. The center of the tumor was formed by dense, adult cancellous bone.

The picture in general was one of quiescence and that of an eburnated osteoma (this section was removed from the lower edge of the tumor and from the roentgenogram it can be seen that this is really a spongy osteoma, eburnated in its periphery).

Ultimate Result.—The patient was discharged well.

CASE 7.—*History.*—A white youth, aged 18, was admitted to the service of Dr. Dandy in March, 1929, complaining of an enormous bony tumor on the vertex of the skull. The family history and personal history were negative.

At the age of 4 years the patient fell and struck his left supra-orbital region. Ten years later, a small, bony tumor developed at the site of the trauma. At 5 years of age, he fell and struck the back of his head. A bony tumor was noticed at the site of this trauma when the patient was 7 years of age. The skin was not lacerated in either case. Both of these lumps gradually increased in size. At about 10 years of age, he was told that he did not have long to live, and since the age of 16 years had had several fainting spells, which were not accompanied by convulsions, aphasia, vomiting or incontinence. Apart from a sense of weight over the apex of the skull, there were no other symptoms.

Physical Examination.—The temperature and pulse were normal. A bony hard, rounded, nontender tumor about the size of a coconut was attached to the left parietal bone. Some dilated vessels were present over the tumor. A similar lump fusing with the one described, but having the shape of a saucer, was present in the left frontal region and shaded imperceptibly into the surrounding skull. The fundi were normal, and the results of the general physical and neurologic examinations and the Wassermann test were negative. There were 10,600 white blood cells and 104 per cent hemoglobin.

Operation (Dr. Dandy).—The osteoma was partially removed. There was considerable bleeding when the thickened vascular periosteum over the tumor was incised. The bone beneath was very vascular and of a soft, mushy, cancellous character. This type of bone extended inward to a quite firm inner table. The bone removed weighed 405 Gm. The majority of the osteoma was removed, including the inner table of the skull.

A diagnosis of osteoma of the skull was made.

Gross Pathology.—The gross specimen consisted of a large domelike mass lying on the removed inner table of the skull. The surface of the dome was covered by a thick fibrous tissue. The body of the mass was composed of cancellous bone through which a knife could be easily plunged. No cortical bone lay on the surface of this tumor. The inner table showed no evidence of new bone formation on its intracranial surface and was smooth except for vessel markings.

Microscopic Pathology.—A section through the outer surface of the tumor showed on the surface a thick hyalinized-like fibrous tissue, giving place to definite preosseous tissue in its deeper layers which was actively participating in the formation of cancellous bony spicules. No cortical bone was seen on the surface of the tumor. Section through the inner table of the skull showed an intact inner table which, however, on its tumor side was transformed into spongy bone.

Ultimate Result.—The patient was discharged well.

Cases from the Literature

Case	Author[a]	Sex	Age	Age of Patient When Tumor First Noted	Duration in Years	Symptoms	Location on External Table	Gross Pathology	Microscopic	Treatment and Results
8	Chassaignac: Thèse de Concours, 1848	?	21	12	9	Symptomless bony hyperostosis which grew slowly at site of trauma; general physical and neurologic examinations gave negative results	Frontal bone encroaching on glabella	Eburnated, 3×1½ inches	.....	Removed; discharged well
9	Wahl: Thèse de Dorpat, 1874	?	12	Infancy	?	Symptomless bony hard tumor, arising without apparent cause; general physical and neurologic examinations gave negative results	Right frontal bone above the orbit	Bony tumor, size of walnut	.....	.....
10	Karowski, 1894, quoted by Marey [b]	?	7	Infancy	?	Symptomless bony hard tumor, arising without cause on skull; three other hyperostoses on face; general physical and neurologic examinations gave negative results	Superior frontal bone	Spherical, bony tumor with large base	.....	.....
11	Reclus: Presse méd., 1894, p. 381	F	21	?	?	Symptomless bony hard tumor	Frontal bone	Bony tumor	.....	Removed
12	Prengreuber,[2e] 1892	F	22	11	11	Symptomless bony hard tumor arising after trauma; general physical and neurologic examinations gave negative results	Left frontal bone	Bony tumor covered by periosteum, the size of a cherry	Periosteum on surface underlying cortical bone, central spongy bone	Removed
13	Demaye: Bull. Soc. anat. de Paris 69 : 841, 1894	F	33	22	11	Symptomless bony hard tumor arising without apparent cause; general physical and neurologic examinations gave negative results	Right frontal bone near inferior extremities of frontoparietal suture	Large base, eburnated bony tumor, size of large walnut covered by periosteum	Normal looking bone continuous with diploe	Removed
14	Hott: Tr. Path. Soc. London, 1850-1851, p. 149	M	40	14	26	Bony hard tumor, apparently symptomless, arising after trauma	Left parietal bone	Broad-based, spongy bony tumor, 2×2 inches; normal inner surface of skull	.....	.....
15	Cooper: Lancet 1 : 628, 1861	F	23	19	4	Bony hard tumor arising without apparent cause; some tenderness was present	Just above mastoid bone	Eburnated bony hard tumor, size of large walnut	.....	Removed
16	Textor: Würzb. med. Ztschr. 6 : 329, 1865	?	66	Infancy	66	Bony tumor, apparently symptomless, arising after trauma	Temporal bone	.....	.....	Died at 66 years of another disease
17	Mauclaire: Bull. Soc. anat. de Paris 7 : 67, 1905	M	29	28	1	Symptomless bony hard tumor; general physical and neurologic examinations gave negative results	Temporoparietooccipital region	Bony tumor covered by thick periosteum with underlying osseous lamellae, continuous with mastoid cells	Osseous tissue on surface underlying cortical bone	Removed
18	Millan: Bull. Soc. anat. de Paris 7 : 72, 1905	F	25	Several years before patient was 15	Over 10 years	Symptomless bony hard tumor; general physicial and neurologic examinations gave negative results	Temporomastoid bone	Eburnated osteoma, no communication with mastoid cells	.....	Removed
19	Marey,[b] 1910	M	65	12	53	Bony hard tumor, symptomless until patient was 60 years of	Upper right parietal bone	Bony hard tumor, 37 cm. in circumfer-	.....	No operation

18	Millan: Bull. Soc. anat. de Paris **7**: 72, 1905	F	25	Several years before patient was 15	Over 10 years	Symptomless bony hard tumor; general physicial and neurologic examinations gave negative results	Temporomastoid bone	Eburnated osteoma, no communication with mastoid cells	.....	Removed
19	Marcy,[9] 1910	M	65	12	53	Bony hard tumor, symptomless until patient was 60 years of age, when irregular headaches and attacks of epilepsy commenced; no loss of consciousness; epilepsy arose after typhoid fever	Upper right parietal bone	Bony hard tumor, 37 cm. in circumference; roentgen evidence; tumor less dense than other cranial bones; "spongiostéome"	.....	No operation
20	Oesterlein: Wurtemb. med. Kor.-Bl., 1832, p. 79	M	76	31	45	Symptomless bony hard tumor arising after trauma; size of bean at onset; grew to size of grape-fruit; general physical examination gave negative results	Frontal bone	Eburnated.....	.....	Removed
21	Bonnet, quoted by Luxembourg [27]	?	..	..	..	Two bony hard tumors	Large one on frontal bone; small one on parietal bone	Irregular surface, spongy bone in center of tumor, inner table slightly depressed	.....	Removed
22	Burns, quoted by Luxembourg [27]	F	32	..	..	Bony hard tumor, apparently symptomless; had grown slowly	Frontal bone	Eburnated bony tumor, size of a large walnut	.....	.....
23	Kretschmann, 1910, quoted by Luxembourg [27]	F	20	..	..	Bony hard tumor, apparently symptomless; history of chronic otitis media	Squamotemporo-occipital bone	Eburnated ivory-like bony tumor, 2.5×2.5 cm.	.....	Removed
24	Kretschmann, 1910, quoted by Luxembourg [27]	F	19	..	..	Bony hard tumor, size of pinhead at first, apparently symptomless	Mastoid bone	Fibrous tissue surface underlying cortical bone	.....	Removed
25	Orator,[10] 1931	F	22	10	12	Bony hard tumor, parietal bone since 10 years of age; second tumor arose in the outer surface of the orbit at 14 years; severe headaches and occasional dizziness for past few years; general physical and neurologic examinations gave negative results; Wassermann reaction negative; skin normal and freely movable	Right parietal bone and right frontal bone above orbit	Bony tumor size of male fist, weighing 470 Gm.; spongy type; inner surface of skull normal; showed markings of vessels	.....	Removed; discharged well
26	Luxembourg [27] 1918	F	19	Birth	19	Bony hard tumor, symptomless; general physical and neurologic examinations negative	Temporoparietal region	Size of male fist; part of tumor ivory-like, especially at edges; central region of tumor spongy	Central spongy bone with abundant fibrous-osseous tissue; adult cortical bone at edges	Removed; discharged well

* Cases 1 to 7 are presented for the first time. Cases 8 to 26 are from the literature.

EFFECT OF MORPHINE ON OBSTRUCTED INTESTINE

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NEW ORLEANS

Even earlier than 1500 B. C. opium was used in the treatment of diseases of the gastro-intestinal tract. In the Papyrus Ebers,[1] the following prescription was suggested "to clear out the body and to get rid of the excrement in the body of a person":

Leaves of the castor oil plant	¼
Dates of the male palm	5/6
Cyperus grass	1/16
Stalk of the poppy plant	1/16
Coreander	1/16
Cold beer	½

Keep moist, strain and take for four days.

At the present time morphine is undoubtedly one of the most valuable drugs which the surgeon has in his armamentarium, and without it or some of the other derivatives of opium, postoperative convalescence would be associated with prolonged and unnecessary suffering. Many surgeons, however, use morphine sparingly because of its supposed inhibiting effect on the intestinal motility and because of the fear of producing or increasing an already existing ileus.

Because of the constipating effect of morphine, which has been considered due to an inhibition of intestinal activity, the drug has been considered by most surgeons almost a specific in limiting the spread of peritoneal infection. In such cases and in those of contamination it has been used in large doses in order to "splint" the bowel. Perusal of some of the more recent textbooks on surgery[2]

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1. Papyrus Ebers, translated from the German by C. P. Bryan, New York, D. Appleton and Company, 1931.

2. Ashhurst, A. P.: Surgery: Its Principles and Practice, ed. 4, Philadelphia, Lea & Febiger, 1931. Blake, J. A.: Peritonitis, in Diseases of the Peritoneum, Nelson Loose-Leaf Living Surgery, New York, Thomas Nelson & Sons, 1928, vol. 5. Stewart, F. T., and Lee, A. E.: Manual of Surgery, ed. 6, Philadelphia, P. Blakiston's Son & Co., 1931. Hartwell, J. A., and Cooper, H. S. F.: Intestinal Obstruction of the Ileus, in Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, 1930, vol. 7. Jones, D. F., and McClure, W. L.: The Peritoneum, ibid. Romanis, W. H. C., and Mitchiner, P. H.: Science and Practice of Surgery, ed. 2, New York, William Wood & Company, 1929, vol. 2.

shows that almost without exception the administration of morphine is suggested in cases of peritonitis because of the supposed inhibiting effect which the alkaloid exerts on the intestines.

The pharmacologic effects of opium and its derivatives, especially as regards their influence on intestinal activity, apparently vary in different species of animals. The majority of textbooks on pharmacology state that one of the chief actions of morphine on the intestinal tract is to decrease peristalsis (Cushney,[3] Solis-Cohen and Gilteus[4] and Wilcox[5]). Sollmann,[6] however, believes that the constipating effect of morphine is due to its action on the pylorus, i. e., spasmodic closure, which causes the food to enter the intestine more slowly than normally. In addition, he is of the opinion that morphine diminishes rectal sensation, which in turn decreases the sensitivity of the defecation reflex.

Considerable experimental work has been done on the effect of morphine on the normal intestine. As early as 1882, Nothnagel[7] found that small doses of morphine decreased intestinal activity whereas larger doses increased it. He believed that the action of the morphine was through the splanchnic nerves and that small doses of morphine stimulated, while large doses paralyzed, the splanchnics. Pal,[8] in 1900, found that opium and morphine invariably produced an increase in intestinal activity in dogs. He observed that the increase occurred even when the nerve supply to the intestine was cut, indicating that the action was on the peripheral ganglions. Magnus[9] showed by roentgenographic studies that the administration of morphine had little effect on the motility of the small intestine, but that by causing marked contraction of the pyloric antrum it produced constipation. Mahlo[10] found from roentgen examination of young persons receiving tincture of opium by mouth that there was considerable decrease in the motility of the small and large intestines. In

3. Cushney, A. R.: Textbook of Pharmacology and Therapeutics, ed. 6, Philadelphia, Lea & Febiger, 1915.

4. Solis-Cohen, S., and Gilteus, T. S.: Pharmacotherapeutics, New York, D. Appleton and Company, 1928.

5. Wilcox, R. W.: Materia Medica and Therapeutics, ed. 12, Philadelphia, P. Blakiston's Son & Co., 1929.

6. Sollmann, T.: Manual of Pharmacology, ed. 3, Philadelphia, W. B. Saunders Company, 1926.

7. Nothnagel, H.: Ueber die Einwirkung des Morphins auf den Darm, Virchows Arch. f. path. Anat. **89**:1, 1882.

8. Pal, J.: Neue Untersuchungen über die Wirkung des Opiums und des Morphins auf den Darm, Wien. med. Presse **41**:2040, 1900.

9. Magnus, R.: Die stopfende Wirkung des Morphins, Arch. f. d. ges. Physiol. **115**:316, 1906; **122**:210, 1908.

10. Mahlo, Arthur: Ueber die Wirkung des Opiums auf den menschlichen Magen-Darmkanal, Deutsches Arch. f. klin. Med. **110**:562, 1913.

the same year, Schapiro,[11] also employing roentgenographic methods, found that the administration of morphine and other opium derivatives exerted little effect on the small intestine. He considered that the constipating effect of these substances was due to the diminished defecation reflex. Trendelenburg [12] found that the addition of morphine and other opium derivatives to perfusion fluids increased the activity of suspended loops of the intestines of dogs and cats but decreased the activity of the intestines of rabbits and guinea-pigs. Tsunemichi,[13] employing the same methods as Trendelenburg, found that if the suprarenal glands were removed or if splanchnicotomy was performed in rabbits, morphine exerted no inhibiting effect on the intestinal activity. Uhlmann and Abelin,[14] working with the isolated intestines of various animals, found that opium preparations in small doses always paralyzed, in large doses stimulated and in very large doses at first stimulated and later paralyzed, the intestine. Contrary to Trendelenburg's observations,[12] they found that the intestines of both rabbits and guinea-pigs, the latter less than the former, were stimulated by the administration of morphine. Plant and Miller,[15] working with Thiry fistulas in dogs, found that the injection of morphine caused marked increases in intestinal tone followed by increases in peristaltic movement. The increases in tone lasted from three to twelve hours. Because they obtained a typical reaction with loops of intestine which had been denervated, and after the administration of atropine, they expressed the belief that the action of morphine is peripheral and is exerted on the plexuses of Meissner and Auerbach. In addition to the experiments with animals, Plant and Miller [15] found that similar effects were obtained by the administration of morphine to human beings. King and Church,[16] working with Magnus' preparations of intestinal musculature, found that the administration of morphine was without effect either on the tone or on the rhythm of the muscle unless large doses were given, which acted as a depressant. Miller and

11. Schapiro, N.: Ueber die Wirkung von Morphium, Opium und Pantopon auf die Bewegungen des Magen-Darm-Tractus des Menschen und des Tieres, Arch. f. d. ges. Physiol. **151**:65, 1913.

12. Trendelenburg, P.: Physiologische und pharmakologische Versuche über die Dünndarmperistaltik, Arch. f. exper. Path. u. Pharmakol. **81**:55, 1917.

13. Tsunemichi, Hayama: The Rôle of the Suprarenals in the Sedative Effect of Morphine on the Intestine, Folia pharmacol. japon. F:10, 1928.

14. Uhlmann, F., and Abelin: Opium, Ztschr. f. exper. Path. u. Therap. **21**:58, 1920.

15. Plant, O. H., and Miller, G. H.: Effects of Morphine and Other Opium Alkaloids on Muscular Activity of Alimentary Canal: Action on Small Intestines in Unanaesthetized Dogs and Man, J. Pharmacol. & Exper. Therap. **27**:361, 1926.

16. King, C. E., and Church, J. G.: The Motor Reaction of the Muscularis Mucosae to Some Drugs, Am. J. Physiol. **66**:428, 1923.

Plant[17] found that even if morphine was given over long periods, tolerance of the intestine for the drug did not develop. Gruber, Crawford, Greene and Drayer[18] found that an antagonism exists between morphine and phenobarbital sodium, and between morphine and pituitary. The loss of tone produced by the administration of phenobarbital sodium could be combated by the administration of morphine. Following the administration of pituitary, morphine caused an increase in intestinal activity. The effects of morphine on the tone of the colon in both animals and human beings were determined by Plant and Miller.[19] Recording balloons were introduced into the lumen of the colon through fistulas. In all instances, the injection of morphine caused an increase in intestinal tone and movement. This stimulation occurred at times several hours after the injection of morphine. There was a return to normal in about eight hours. These authors expressed the belief that one of the constipating effects of morphine is due to the fact that because of the increased tone in the colon food is retained therein for longer periods, so that water is absorbed, making the stool less bulky. Similar results were obtained by Gruber and Robinson,[20] who found that the first injection of morphine always caused increases in tone and in amplitude of the intestine, whereas repeated injections tended to cause decreases in tone and in rhythmic contraction. Gruber, Greene, Drayer and Crawford[21] found that morphine and atropine acted antagonistically on intestinal musculature. The decrease in intestinal tone produced by the injection of atropine was combated by subsequent injections of morphine, whereas the injection of atropine at the height of an increased intestinal activity produced by morphine caused a marked drop in tone, the loss usually being recovered slightly.

17. Miller, G. H., and Plant, O. H.: Effect of Morphine and Other Opium Alkaloids on Muscular Activity of Alimentary Canal: Influence of Continued Administration of Morphine and of Withdrawal on Contractions of Small Intestines of Dogs, J. Pharmacol. & Exper. Therap. **28**:241, 1926.

18. Gruber, C. M.; Crawford, W. M.; Greene, W. W., and Drayer, C. S.: The Effect of Sodium Phenobarbital and the Antagonism of Morphine to Phenobarbital and to Pituitary Extract in Intact Intestine in Non-Anaesthetized Dogs, Proc. Soc. Exper. Biol. & Med. **42**:27, 1927.

19. Plant, O. H., and Miller, G. H.: The Effect of Morphine and Some of the Other Opium Alkaloids on the Muscular Activity of the Alimentary Canal: IV. Action of Morphine on the Colon of Anaesthetized Dogs and Man, J. Pharmacol. & Exper. Therap. **32**:437, 1928.

20. Gruber, C. M., and Robinson, P. I.: Intestinal Activity in Unanaesthetized Dogs as Influenced by Morphine and Papaverine, J. Pharmacol. & Exper. Therap. **37**:101, 1929.

21. Gruber, C. M.; Greene, W. W.; Drayer, C. S., and Crawford, W. M.: Further Studies on the Effect of Morphine Sulphate, Atropine Sulphate, and Hyoscine Hydrobromide upon the Intact Intestine in Unanaesthetized Dogs, J. Pharmacol. & Exper. Therap. **38**:389, 1930.

Gruber and Pitkin,[22] working with Thiry fistulas and isolated segments of intestine, found that morphine invariably increased the activity. Dvorak, Carlson, Erickson, Smith and Wangensteen,[23] in experimental and clinical observations, found that injections of morphine produced in the normal bowel of both human beings and dogs immediate increases in intestinal tone followed by increases in peristaltic activity. These were more marked in the small than in the large bowel. In intestinal obstruction, a similar response to the administration of morphine was observed. In five patients and ten animals with intestinal obstruction there were evidences of increased activity as determined by increased peristaltic sounds. Gruber, Bryan and Richardson [24] found that morphine, when injected intravenously, given by mouth or inserted into the lumen of the intestine through a Thiry fistula, caused an increase in intestinal tone and temporary cessation of peristalsis in animals. Wilen and Dragstedt [25] found that in the presence of peritonitis injections of morphine caused an increase in intestinal movement.

EXPERIMENTS

Because of the widespread use of morphine in surgical practice, and because most of the recent studies have been made on normal and not on obstructed intestines, the present investigation was undertaken. Dogs were chosen as the experimental animals. Twenty-three observations concerning the effect of morphine on obstructed intestines were made in eighteen dogs. In three additional animals, three observations were made of the effect of a mixture of the hydrochlorides of the opium alkaloids on obstructed intestines. Four observations were made on animals with obstruction of forty-eight hours' duration and nineteen on animals with obstruction of seventy-two hours' duration. The three observations in which the mixture of the hydrochlorides of the opium alkaloids was used were made on animals with obstruction of seventy-two hours' duration. The obstruction was produced as follows:

With the animal under ether anesthesia, and with aseptic technic, a laparotomy was performed. The terminal ileum was obstructed by tying binding tape tightly

22. Gruber, C. M., and Pitkin, Garrett: Further Observations on the Effect of Pituitary Extract and Morphine Sulphate upon Excised Dogs' Intestines, J. Pharmacol. & Exper. Therap. **38**:401, 1930.

23. Dvorak, H. J.; Carlson, H. A.; Erickson, T. C.; Smith, V. D., and Wangensteen, O. H.: Influence of Morphine on Intestinal Activity in Experimental Obstruction, Proc. Soc. Exper. Biol. & Med. **28**:434, 1931.

24. Gruber, C. M.; Bryan, W. T., and Richardson, L. R.: Response of Intact Small Intestine in Non-Anaesthetized Dogs to Cathartic Agents, to Morphine and Atropine, Proc. Soc. Exper. Biol. & Med. **28**:470, 1931.

25. Wilen, C. J., and Dragstedt, C. A.: Action of Morphine on Intestine in Peritonitis, Proc. Soc. Exper. Biol. & Med. **28**:1056, 1931.

around the terminal portion of the ileum. Care was taken not to tie the tape so tightly that necrosis would result. After varying periods, from twenty-four to seventy-two hours, the animal was again operated on. Two tubes were introduced into the dilated obstructed intestine proximal to the obstruction; one served as an enterostomy tube, and the other, which was introduced proximal to the enterostomy tube, carried a rubber balloon. The second, or recording, tube was connected with a tambour so that kymographic tracings of the activity of the bowel could be recorded. The animal was placed in a bath of salt solution, as described in previous publications,[26] and kymographic tracings were made.

OBSERVATIONS

Four observations were made on three animals with obstructions of forty-eight hours' duration. In two experiments, ⅛ grain (7.5 mg.) of morphine was injected subcutaneously; in the other two experiments, ¼ grain (15 mg.) was given. There was increased activity in three instances (75 per cent), and no change occurred in one (25 per cent). In the latter instance, however, the morphine was given at the height of an increase in activity caused by a previous injection of morphine, and therefore one probably should consider that there was no change. The average increase in tone was 83.3+ mm. (fig. 1). The average increase in amplitude was 28.3 mm., and the average duration of the activity was thirty-two and six tenths minutes (fig. 2). The activity persisted longer than these figures would indicate, because in two instances the intestine was still active at the termination of the experiment. The average dose was 2.6 mg. per kilogram of body weight. There was no change in blood pressure.

Nineteen observations were made in fifteen dogs with obstructions of seventy-two hours' duration. Five of these could not be used because the intra-intestinal balloon leaked. In one of the fourteen observations that were used, the balloon was leaking. In another, the morphine was given after the administration of 10 per cent dextrose solution, which we[27] have shown to exert an inhibiting effect on the intestine. In thirteen (92.8 per cent) there were increases in intestinal activity, and in one (7.2 per cent) there was no change. The average increase in tone in the experiments in which there was normal activity was 43.1 mm. (figs. 3 and 4). In one instance, the increase was much greater than this, as the lever passed off the kymographic drum. The average increase in amplitude was 13 mm. (fig. 5). The average duration of the increased activity was twenty-eight and three tenths minutes plus. That the duration was much longer is proved by the

26. Ochsner, Alton; Gage, I. M., and Cutting, R. A.: Comparative Value of Splanchnic and Spinal Analgesia in the Treatment of Experimental Ileus, Arch. Surg. **20**:802 (May) 1930.

27. Gage, I. M.; Ochsner, Alton, and Cutting, R. A.: Effect of Insulin and Glucose on Normal and Obstructed Intestine, Proc. Soc. Exper. Biol. & Med. **29**:264, 1931.

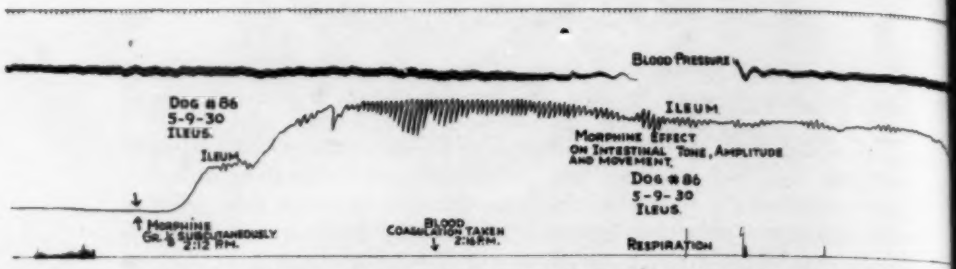

Fig. 1.—Kymographic tracing showing the stimulating effect of morphine (⅛ grain [7.5 mg.] injected subcutaneously) on an intestine obstructed for forty-eight hours. As indicated by the arrow on the left side, the morphine was injected at a time when the bowel was motionless. Within thirty seconds there was a rapid rise in tone, which was followed by increased movement. The increased tone persisted.

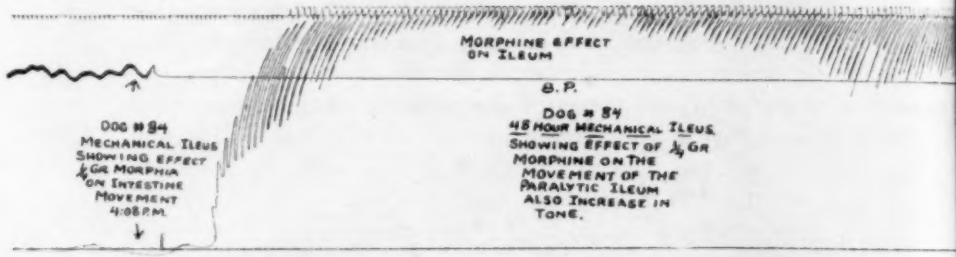

Fig. 2.—Kymographic tracing showing the effect of morphine (¼ grain [15 mg.]) on the activity of an intestine obstructed for forty-eight hours. The arrow at the left of the tracing indicates the injection of morphine. Within one minute after the injection there was a marked rise in tone, associated with a definite increase of movement. The rise in tone was so great that the writing lever struck against the clock lever. The action was prolonged.

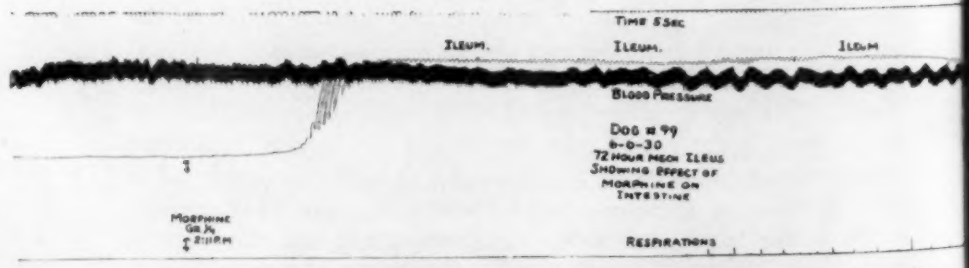

Fig. 3.—Kymographic tracing showing the effect of morphine (¼ grain [15 mg.]) on the activity of an intestine obstructed for seventy-two hours. The arrow at the left of the tracing indicates the injection of morphine. Within approximately a minute and a half after the injection there was a sudden increase in tone, which was associated with only a slight increase in amplitude. The increased tone persisted.

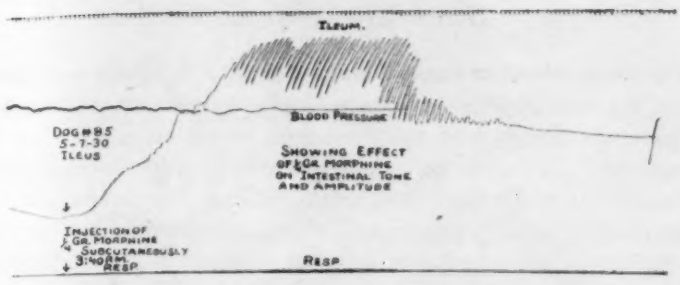

Fig. 4.—Kymographic tracing showing the effect of morphine (¼ grain [15 mg.]) on the activity of an intestine obstructed for seventy-two hours. The arrow at the left of the tracing indicates the injection of morphine. Within one minute after the injection there was a sudden rise in tone, which reached its maximum after approximately two minutes and was then associated with a marked increase in movement. After four minutes the tone fell somewhat; it reached a higher level than before the injection of morphine and persisted at this level.

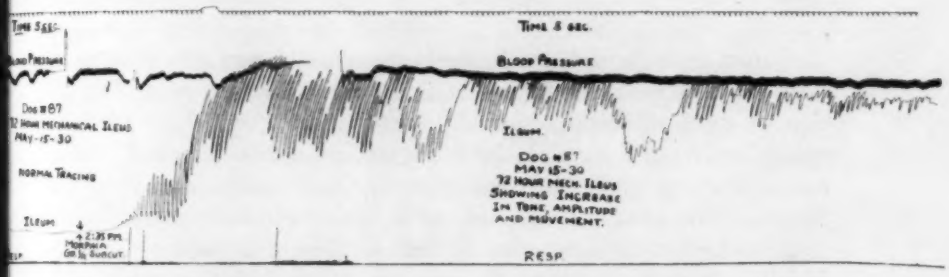

Fig. 5.—Kymographic tracing showing the effect of morphine (¼ grain [15 mg.]) on the activity of an intestine obstructed for seventy-two hours. The arrow at the left of the tracing indicates the injection of morphine. Within one minute after the injection there was a marked increase in intestinal movement with a rise in intestinal tone, which persisted until the end of the experiment.

Fig. 6.—Kymographic tracing showing the effect of subcutaneous injection of a mixture of opium alkaloid hydrochloride (⅓ grain [20 mg.]) on the activity of an intestine obstructed for seventy-two hours. The arrow at the extreme left of the tracing indicates the injection of the preparation. Within two minutes after the injection there was a sudden rise in tone with an increase in movement. The bowel became tonically contracted, but later the tonic spasm was replaced by periods of increased intestinal movement.

fact that in six of the thirteen observations in which there was increased activity, the intestine was still active at the termination of the observation. The average dose of morphine used was 1.8 mg. per kilogram of body weight. There was no change in the blood pressure except in two observations in which there was a gradual fall. In three animals with obstructions of seventy-two hours' duration, observations were made of the effect of the administration of a mixture of the hydrochlorides of opium alkaloids. In each instance, ⅓ grain (20 mg.) was administered. There was an average increase of tone of 36.6 mm., with an average increase in amplitude of 14.6 mm., and the average duration of the increased activity was twenty-two minutes (fig. 6). In two of these animals, however, dextrose solution was given at the height of activity, which undoubtedly influenced the effect of the mixture of the hydrochlorides of the opium alkaloids. The average dose of the opium alkaloid preparation used was 2.4 mg. per kilogram of body weight.

COMMENT

From these experimental observations and from those of others, both experimental and clinical, it is apparent that the present conception of most clinicians, especially surgeons, that morphine and other opium derivatives exert an inhibiting action on the intestine is incorrect. That morphine is constipating is well known and cannot be denied. The constipating effect of opium derivatives is undoubtedly responsible for the erroneous conception that these substances inhibit intestinal activity, whereas, as suggested by Sollmann,[6] the constipating effect is probably due to spasmodic closure of the pylorus and diminished rectal sensitivity. It is possible, as suggested by Plant and Miller,[19] that dehydration of the intra-intestinal contents may be a factor. Plant and Miller [19] expressed the belief that, as a result of the increased intestinal tone, food may remain in the intestine for longer periods, which permits extraction of water.

Most surgeons, even though they realize the value of the postoperative use of morphine, feel that it should be employed cautiously, because of the danger of inhibiting intestinal peristalsis. We are convinced from our own clinical experience that morphine in no way favors ileus. On the contrary, its administration has been beneficial in cases of ileus. Previously we felt that the analgesic properties of morphine were responsible for the improvement noted in patients with ileus, but we now realize that the stimulating action is also important. In the present investigation all observations were made on obstructed intestines. The beneficial results obtained from the administration of opiates in cases of peritonitis are not due to the "splinting" of the bowel, but are probably due to the analgesic and sedative properties

of the drugs. Even though morphine not only does not inhibit intestinal movement but actually increases it, it is probable that in the presence of intense peritoneal irritation, such as is caused by peritonitis, morphine exerts little or no stimulating effect. This probably explains why opiates are not harmful in peritonitis.

The efficacy of morphine as a stimulant of intestinal movement is demonstrated by comparing results obtained in experimental ileus by the administration of morphine and of hypertonic salt solutions. The latter, since the original observations of Hughson and Scarff [28] and Ross,[29] have been known to exert a powerful stimulating effect on the motility of the intestine. We [30] have demonstrated, both clinically and experimentally, that hypertonic Ringer's solution intravenously administered is more efficacious in stimulating intestinal activity than hypertonic solutions of sodium chloride. Whereas the administration of morphine to animals with intestinal obstruction of forty-eight hours' duration caused average increases in tone and amplitude of 83 mm. and 28 mm., respectively, the intravenous administration of hypertonic Ringer's solution caused average increases in tone and amplitude of 62 and 11 mm., respectively. The average duration of the increased activity in the experiments with morphine was thirty-two minutes, and in those with Ringer's solution, twelve and four-tenths minutes. The results obtained in the two investigations are not entirely comparable because of the difference in the number of observations, four being made with morphine and fourteen with Ringer's solution. The administration of morphine to animals with obstruction of seventy-two hours' duration caused average increases in intestinal tone and amplitude of 43 and 13 mm., respectively, whereas in similar experiments the intravenous injection of hypertonic Ringer's solution caused average increases in tone and amplitude of 64 and 18 mm., respectively. The average duration of the increased activity in the experiments with morphine was twenty-eight minutes, and in those with Ringer's solution, twenty minutes.

It is evident that morphine is a definite stimulant to intestinal activity, and that it can even be compared with hypertonic salt solution in its efficacy, although on intestines obstructed for seventy-two hours, its effect was less marked than that of the salt solution.

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28. Hughson, W., and Scarff, J. E.: Influence of Intravenous Sodium Chloride on Intestinal Absorption and Peristalsis, Bull. Johns Hopkins Hosp. **35**:197, 1924.

29. Ross, J. W.: Hypertonic Saline in Adynamic Ileus, Canad. M. A. J. **16**: 241, 1926.

30. Ochsner, Alton; Gage, I. M., and Cutting, R. A.: Treatment of Experimental Ileus by Hypertonic Saline Solutions, Proc. Soc. Exper. Biol. & Med. **29**:911, 1932; Influence of Hypertonic Salt Solution on the Motility of Normal and Obstructed Intestine: An Experimental Study, Arch. Surg., to be published.

CONCLUSIONS

1. Contrary to the opinions of most clinicians, opium derivatives stimulate rather than inhibit the activity of the small intestine.

2. The present investigation demonstrates that the administration of morphine and of a mixture of the hydrochlorides of the opium alkaloids to animals with intestinal obstruction greatly increases the activity of the intestine.

FIFTY-SECOND REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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CONGENITAL DEFORMITIES

Early Treatment of Congenital Dislocation of the Hip.—Putti [1] reviewed 119 cases of congenital predislocation of the hip. Complete cure has been obtained in 113. The author advocated routine roentgen examination of the hips of infants in order that the condition might be recognized early and treatment begun immediately by the abduction method.[2] This method was applicable to all children under 12 months of age.

ENDOCRINE REGULATION OF CALCIUM METABOLISM

Rôle of Parathyroid Glands in Diseases Associated with Demineralization of the Human Skeleton.—Compere,[3] from his observations in cases of generalized osteitis fibrosa, Paget's disease and polyarthritis,

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This report of progress in orthopedic surgery is compiled from a review of 152 articles selected from 258 titles appearing in the various medical journals approximately between March 25, 1933, and July 1, 1933. Only the papers that seemed to represent progress were selected for review.

1. Putti, V.: J. Bone & Joint Surg. **15**:16, 1933.
2. Putti, V.: J. Bone & Joint Surg. **11**:838, 1929.
3. Compere, E. L.: J. Bone & Joint Surg. **15**:142, 1933.

concluded that the first condition was always associated with an adenomatous tumor of the parathyroid gland and was characterized by a high serum calcium content, low plasma phosphates, increased excretion of calcium in the urine and a negative calcium balance. He stated that there was no good evidence that Paget's disease was caused by hyperparathyroidism; that ankylosing polyarthritis was not caused by hyperparathyroidism, and that the atrophy of the skeleton in polyarthritis was due to disuse.

Regulation of Blood Calcium Level Through Parathyroid Hormone.—Spiegler and Stern [4] reported their observations on the use of parathyroid hormone in rabbits, in normal persons and during pregnancy. After injection of parathyroid hormone, there was a rise in the calcium level which was most marked in the experimental animals. The rise in the blood calcium took the form of a curve with its maximum in from one to two hours. No relationship could be found between the decline of the curve and the amount of hormone given. The rise of the blood calcium was not considered by the author to be a specific action of the hormone since a rise could be produced by other substances such as prolan or epinephrine. Changes in galvanic excitability did not run parallel with the amount of blood calcium. The authors were led to conclude that the parathyroid hormone in both normal and pathologic states acted as a regulator in attempting to maintain the serum calcium at a normal level.

OSTEOMYELITIS

Early Diagnosis of Acute Osteomyelitis of the Spine.—Esau [5] called attention to the presence of edema and purulent collections in vertebral osteomyelitis as shown in roentgenograms. Shadows similar to those seen in tuberculous spondylitis were shown in illustrations in 2 cases. In both of these pus was obtained on incision, and the shadows disappeared on recovery. In one case the lower dorsal vertebrae were involved; in the other, the low lumbar vertebrae.

Acute Osteomyelitis of the Vertebrae.—Klein [6] studied 18 cases of acute osteomyelitis of the vertebrae; 16 of these he reported in detail. All were metastatic from boils, previous chronic osteomyelitis, pneumonia, cellulitis and phlebitis. He divided his patients into four groups: (1) those showing abscess formation anywhere along the spine; (2) those presenting complaints referable to the nervous system due to involvement of nerve roots; (3) those presenting only pain in the back and fever, and (4) those suffering from widespread bac-

4. Spiegler, R., and Stern, K.: Ztschr. f. Geburtsh. u. Gynäk. **104**:250, 1933.
5. Esau, P.: Deutsche Ztschr. f. Chir. **239**:615, 1933.
6. Klein, H. M.: Acute Osteomyelitis of the Vertebrae, Arch. Surg. **26**:169 (Feb.) 1933.

teremia and multiple abscesses. In 10 patients the processes of the vertebrae were involved. The roentgenograms were frequently negative. Treatment was always surgical, i. e., drainage of the osseous focus.

Osteomyelitis of the Scapula.—Giubal and Montagne [7] made a systematic study of the various types of osteomyelitis of the scapula. How much their study was based on actual cases is hard to determine, although some case histories were given. They found that osteomyelitis of the scapula occurred as a rule in the second decade of life, that it was twice as common in males as in females, and that the pathogenic organism in all cases was Staphylococcus aureus which gained entrance in most cases through the skin. The different types of osteomyelitis were classified according to the location: (1) supraspinous; (2) infraspinous; (3) subscapular; (4) articular; (5) axillary, and (6) diffuse periscapular. Diagnosis, treatment and complications were discussed under each of the six headings.

Peculiarities of Osteomyelitis in Early Childhood.—Paschlau [8] studied the peculiarities of osteomyelitis in early childhood at the Children's Hospital of Berlin. In 42 cases of osteomyelitis of the long bones in infants, diaphyseal localization was observed only 5 times. Almost always the disease was found in the metaphysis. Often purulent arthritis in the nearby joints occurred, particularly when the epiphysis was for the most part intra-articular, by spreading along the epiphysis, but not through the cartilage. The bones most frequently affected were the femur, humerus and tibia. The proximal ends were most commonly involved. The short bones and flat bones were involved frequently in infants, with decreasing frequency with each year of age. Suppurative arthritis was the commonest complication and was observed in 41 per cent of the cases seen in infants. Separation of the epiphysis was the next most common complication, occurring in 20 per cent of the infants. Bowing at the metaphysis was not infrequently seen. Secondary foci of osteomyelitis were not necessarily of grave prognosis; of 7 infants with two foci, 4 recovered. It was not the number of septic metastases but their localization which modified the prognosis. The least serious localizations were in bones, muscles and joints. Of the 13 fatal cases, 9 were cases of extensive osteomyelitis with metastases to vital organs. In these, abscess of the lung occurred 3 times, generalized pyogenic abscesses 4 times, and pneumonia, mastoiditis and meningitis, once. In the other 4 cases metastases occurred late; in one case, endocarditis, and in another, pericarditis, with a progressive decrease in resistance. The formation of sinuses and sequestrums were uncommon, but metastases to joints and other tissues were the characteristics

7. Giubal, A., and Montagne, J.: Rev. de chir. **52**:268, 1933.
8. Paschlau, G.: Monatschr. f. Kinderh. **55**:280, 1933.

of osteomyelitis of infancy. One case of osteomyelitis of the vertebra in a 21 month old infant was observed. Bacteriologic investigations were not recorded. The operative procedure was usually limited to opening the abscess at the metaphysis without disturbing the bone. Further high temperature was usually due to metastases to the joint or to other tissues.

POLIOMYELITIS

Prevention of Poliomyelitis—In a résumé of the investigation of the immunologic phenomena in poliomyelitis, Flexner [9] concluded that whether or not it could be definitely proved that convalescent serum therapy was of benefit, the patient should be given the serum, as the choice lay between no therapy and a kind of intervention believed to be harmless and perhaps sometimes useful in this disease. The advantage of passive serum protection during epidemics seemed to have been proved in part, and the possible future of active immunization was considered.

CHRONIC ARTHRITIS

Surgical Treatment of Osteo-Arthritis of the Hip.—Operative treatment was considered by Groves [10] to be specially indicated in monoarticular osteo-arthritis of comparatively young patients and in those cases in which trauma has been a causative factor and pain a prominent result. Different operative procedures were suggested to meet various requirements; cheilotomy, in cases of marked osteophytic outgrowths resulting from trauma and confined to one hip; arthroplasty, by reducing the head or removing the inferior part of the acetabulum, for hips with deep sockets when the head and neck were enlarged so that the joint became "seized"; arthrodesis, in single painful hips; excision, on the worst side in cases of bilateral stiff and painful hips, and osteotomy, in cases of coxa vara or subluxation.

Cystic Nodules of Terminal Finger Joints.—Nachlas [11] reported a study of cystic nodules of the terminal phalanges of the finger joints. He removed and studied 28 specimens from 25 cases and treated another group symptomatically. He concluded that the gelatinous filled cysts represented a preosseous stage of Heberden's nodes. They showed a high calcium content but no uric acid or urates. He recommended removal of the cysts under local anesthesia (ethyl chloride) for cosmetic reasons.

Roentgenotherapy in Arthritis.—Langer [12] advocated high voltage roentgenotherapy as an important aid in the treatment of atrophic arthri-

9. Flexner, S.: Brit. M. J. **1**:132, 1933.

10. Groves, E. W.: Brit. M. J. **1**:3, 1933.

11. Nachlas, I. W.: Cystic Nodules of Terminal Finger Joints, Arch. Surg. **25**:1067 (Feb.) 1932.

12. Langer, H.: Radiology **20**:78, 1933.

tis. In addition to treating involved joints directly, he also gave paravertebral treatments in order to influence the sympathetic ganglions supplying the affected areas. The rationale of this procedure was based on the opinion that the x-rays have some effect on the vegetative nervous system which produced better circulation and tissue metabolism. Beneficial results were observed in patients who did not receive any other sort of treatment. Langer advocated the use of the x-rays before attempting any surgical measures on the sympathetic ganglions. In addition to their effect on the sympathetic nervous system, the x-rays lessened anaphylactic reaction, had a direct effect on lymphocytes and leukocytes, reduced general inflammation and pressure on nerve sheaths and had an analgesic effect. The technic and dosage were described.

[ED. NOTE.—The place of roentgenotherapy in the treatment of arthritis is still in question. We advise caution in its use until more definite knowledge of its effect on diseased joints is obtained.]

NEOPLASMS

Chondroma of the Intervertebral Disk.—Alpers, Grant and Yaskin [13] reported a single case of "chondroma" of the intervertebral disk in a woman. Symptoms came on after a severe fall on the coccyx and were relieved completely by operative removal of the tumor. They found 35 such cases in the literature: of these, 46 per cent involved the cervical area; 37 per cent the lumbar region, and 17 per cent the thoracic region. The authors felt that these tumors developed as an outgrowth of the fibro-cartilaginous annulus fibrosus rather than from the nucleus pulposus since they were comprised chiefly of fibrocartilage. A worthwhile review of the entire subject and of the current literature was given.

Early Diagnosis of Malignant Disease of the Bone.—The complexity of early accurate diagnosis of osteogenic sarcoma, of either the osteoplastic or the osteolytic variety, was emphasized by Brockman,[14] who took the salient points to be: pain, which was more severe if the periosteum remained intact; rapidity of growth; tactile sensation, and roentgenographic examination. The importance of excluding gummatous osteitis was mentioned, but biopsy in such cases was condemned. In doubtful cases roentgenotherapy was advised, not as a curative, but as a diagnostic, measure, since under its influence, for a time at least, sarcomas, as opposed to inflammatory conditions, showed an increase of bone formation. Primary malignant disease of the spine was rare, and although secondary malignant deposits were common, if the primary focus in these cases was unknown, the diagnosis might be somewhat difficult. Secondary growths from a hypernephroma were most commonly found

13. Alpers, B. J.; Grant, F. C., and Yaskin, J. C.: Ann. Surg. **97**:10, 1933.
14. Brockman, E. P.: Practitioner **130**:199, 1933.

in the greater trochanter and bones of the pelvis, and usually exhibited a marked pulsation which in some cases facilitated the differentiation from secondary carcinomatous deposits.

THE BACK

Lumbar and Lumbosacral Diarthrodial Joints.—From the examination of 44 skeletons, Odgers [15] concluded that the hypersthenic form of articular facets in the lumbar region was more common in females, and the asthenic in males. This was true to a less marked extent in the lumbosacral joints. The superior articular processes began to open at the third lumbar vertebra, and in the vertebrae below this level the tendency of the articular surfaces was to increase in inclination toward the frontal plane. The difference in degree of inclination of the articular facets was due, he suggested, to variations in development and to the activity of the multifidus spinae muscle.

Accessory Articular Process of the Lumbar Vertebra.—Rendich and Westing [16] observed "accessory articular processes" in 5 patients. Two cases of this anomaly had been reported in the German literature. There was a separate ossicle occurring at the lower end of the articular process of the second and third lumbar vertebrae. It was distinguishable from fracture by the absence of a history of trauma and by the roentgenologic appearance. In one case the variation was bilateral.

Significance and Treatment of Sciatic Pain.—Craig and Ghormley [17] summarized the various causes for sciatic pain and then discussed the treatment in those cases in which no known cause could be found. One group of patients was treated in the hospital and another group given ambulatory treatment. In the first group the results of rest, diathermy, Buck's extension, intravenous injection of foreign protein and elimination of foci of infection with and without epidural injections were considered. For the second group the results of epidural injections, sacro-iliac belts and diathermy alone and in various combinations were studied. A fairly high percentage of patients receiving institutional care were completely relieved of their symptoms. Fewer ambulatory patients were relieved but enough to make this sort of treatment worth while when hospitalization was not feasible.

SURGERY OF THE BONES AND JOINTS

Operative Treatment of the Ankylosed Joint.—Campbell [18] reviewed an extensive experience (325 cases) with arthroplasty of various types

15. Odgers, P. N. B.: J. Anat. **67**:301, 1933.
16. Rendich, R. A., and Westing, S. W.: Am. J. Roentgenol. **29**:156, 1933.
17. Craig, W., and Ghormley, R.: Significance and Treatment of Sciatic Pains, J. A. M. A. **100**:1143 (April 15) 1933.
18. Campbell, W. C.: Surg., Gynec. & Obst. **55**:747, 1932.

and regions. He considered in detail the indications and contraindications, operative technic, postoperative care, complications and end-results. The paper gave a concise summary of the present state of knowledge concerning this type of procedure. The article should be read in detail.

Operative Arrest of Longitudinal Growths.—At the University of Chicago Clinic 34 patients were operated on for arrest of growth of an extremity because of inequality in length. The operation consisted of "epiphyseo-diaphyseal fusion." The technic of this procedure was described by Phemister.[19] Among the common conditions resulting in inequality of length of extremities were: (1) fractures involving the epiphysis; (2) infection of the joints with epiphyseal destruction; (3) infections of the bones; (4) tumors of the bone; (5) congenital disturbances and (6) infantile paralysis.

Operative Fixation of Tuberculous Hips in Children.—Wilson [20] made a preliminary report of a study of 33 patients on whom 38 operations were performed to secure ankylosis in tuberculosis of the hip. The operation called "iliofemoroplasty" consisted in turning down from the ilium a wide flap of bone into a slot between the trochanter and the femoral neck. Wilson advocated the operation at any age, since he felt that it did not interfere with growth. Fusion was not done in any case until the diagnosis was established by either biopsy or inoculation into guinea-pigs. Twenty-seven of 33 patients obtained ankylosis as shown both clinically and by roentgenograms. The position of fixation was from 15 to 20 degrees flexion and 10 degrees abduction.

Combined Intra-Articular and Extra-Articular Arthrodesis for Tuberculosis of the Hip Joint.—Henderson [21] reported the end-results in 35 cases of tuberculous hips in which fusion was employed. The ages of the patients ranged from 9 to 48 years. Twenty-seven, or 73 per cent, were between the ages of 10 and 30 years. Operation was performed in 34 cases in the chronic stage of the disease; the thirty-fifth case was in the subacute stage. In 19 patients a combination of the intra-articular and extra-articular methods with a bone graft was used. In 16 cases fusion was attempted by extra-articular methods. Bony union was obtained in 91.4 per cent; the average time before bony union was secured was eight and four-fifths months. Henderson felt that a combination of the intra-articular and extra-articular methods with bone graft was the most effective procedure.

Operative Treatment of Paralytic Genu Recurvatum.—Campbell and Mitchell [22] devised a new operation for the treatment of genu recurvatum

19. Phemister, D. B.: J. Bone & Joint Surg. **15**:1, 1933.
20. Wilson, J. C.: J. Bone & Joint Surg. **15**:22, 1933.
21. Henderson, M. S.: J. Bone & Joint Surg. **15**:51, 1933.
22. Campbell, W. C., and Mitchell, J. I.: Ann. Surg. **96**:1055, 1932.

resulting from infantile paralysis. The operation consisted in fusing the inferior portion of the patella to the anterior aspect of the head of the tibia so that the knee was blocked in complete extension or in a few degrees of hyperextension. Seven patients had been operated on with satisfactory results. In 1, the operation was performed on both knees. The authors felt that the results obtained were superior to those following supracondylar osteotomy of the femur and thought that the effect was more permanent than that secured by any form of ligamentous fixation.

[Ed. Note.—The effect of bone block operations on the knee has not been sufficiently tested to allow definite conclusions to be drawn. There may be danger of traumatic arthritis developing later and also the possibility of recurrence of the deformity due to strain on the graft.]

Extensive Loss of Tibial Diaphysis; Tibiofibular Grafting.—Girdlestone and Foley[23] described a case with extensive loss of the tibial diaphysis through osteomyelitis. Treatment consisted of buttressing the fibula, which was left in its normal position, against the remaining proximal and distal portions of the tibia. From the other tibia one long and two short osseous grafts and one large osteoperiosteal graft were taken. The long graft was laid on the exposed fibular ends within the raised periosteum; the two short grafts were implanted into the tibial ends and bridged over to the fibula; the osteoperiosteal graft was placed over all, thereby completing the periosteal sheath. Plaster fixation for five months was followed by the use of a modified Delbert's walking plaster. Two years later there was no shortening, and the patient was leading a normal life.

Stump Lengthening Through Transplantation of Bone.—Kraus[24] reported the lengthening of a functionally useless humeral stump in a patient with a humerus which was only 13 cm. long with muscles which extended 6 cm. farther distally. The author lengthened the stump 5 cm. by driving a portion of one fibula into the reamed-out marrow cavity of the humerus. The functional result was excellent.

23. Girdlestone, G. R., and Foley, W. B.: Brit. J. Surg. **20**:467, 1933.
24. Kraus, H.: Deutsche Ztschr. f. Chir. **240**:237, 1933.

(To be Concluded)